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Clinicopathological Characteristics of Acute Pyelonephritis with or without Renal Failure and Current Status of Antimicrobial Susceptibility

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Abstract

Acute pyelonephritis (APN) is the most common bacterial infection involving the upper urinary tract system, including the renal parenchyma and pelvis. Complications of APN include renal abscess, septic shock, and renal impairment, including AKI. At the same time, antibiotic resistance of uropathogens resulted in unfavorable clinical responses in APN. The objective of the study was to evaluate the clinical characteristics of patients with APN and antimicrobial susceptibility of causative bacteria. It was a cross-sectional type of observational study which included 100 diagnosed patients of APN admitted into the department of nephrology, Rajshahi Medical College Hospital, Rajshahi, from January 2018 to December 2018. In both males and females, *E. coli* was the major causative bacteria (51.1% vs. 48.9%). Renal failure was present in 87% of patients, and among them, AKI was present in 81.6% and CKD in 18.4%). Infection with *klebsiella* was significantly more common among CKD patients as compared to AKI ($p<0.05$). Commonly used antibiotic ceftriaxone was found significantly resistant in the case of *E. coli* ($p<0.01$) and *klebsiella* ($p<0.05$). In the majority of cases (>50%), *E. coli* was susceptible to nitrofurantoin, amikacin, imipenem, meropenem, and piperacillin-tazobactam. Resistance to antibiotics may complicate the condition. Antibiotic resistance to several commonly used antibiotics

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Introduction

The second most common bacterial infection in the human population is urinary tract infection (UTI)). It is also one of the most frequently occurring nosocomial infections.[1] The annual global incidence of UTI is almost 250 million. Approximately 35% of all hospital-acquired infections are contributed by UTI. [1,2] It is the most common bacterial infection ranging from asymptomatic to severe sepsis. Acute pyelonephritis (APN) is an infection of the upper urinary tract, especially the renal parenchyma and renal pelvis. Misdiagnosis may lead to sepsis, renal abscess, and chronic pyelonephritis that may cause secondary hypertension and renal failure. APN occurs in at least 250000 adults per year in the United States.[3] It is the most severe form of UTI.[4,5]It often requires hospitalization and prolonged therapy, and when accompanied by bacteremia, APN has a mortality rate of 10% to 20%. [6–9]

In acute infection, *E. coli* is the most frequent infecting organism. But the prevalence of antibiotic-resistant organisms such as *Klebsiella,*

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Proteus, Serratia, Enterobacter, *Pseudomonas* increases in complicated UTIs. Among Gram-positive bacteria, *S. saprophyticus, E. faecalis, S. agalactiae, S. pyogenes, S. aureus* are usually present and resistant to a variety of antibiotics. [8,10] The rate of antibiotic resistance is high among uropathogens. The frequency of resistance to antibiotics is directly linked to irrational use of antibiotics and use of antibiotics used in inadequate dose and duration. Treatment of UTI is often started empirically, and therapy is based on information determined from the antimicrobial sensitivity pattern of the urinary tract pathogens in a given community.[11,12] Nowadays, more and more drug-resistant strains of uropathogens have been isolated in patients with APN admitted to hospital than before. Ongoing research on susceptibility patterns of uropathogens is necessary for the precise choice of empirical antibiotics.

Materials and Methods

This was a cross-sectional type of observational study on 100 diagnosed patients of culture-positive APN admitted to the department of nephrology, Rajshahi Medical College Hospital, Rajshahi, Bangladesh, from January 2018 to December 2018. In addition to the clinical diagnosis, patients were required to meet more than 3 of the following five criteria: 1) clinical symptoms of APN (chilling, nausea, vomiting, flank pain); 2) costovertebral angle tenderness; 3) leukocytosis (higher than 10,000/μL); 4) fever (higher than 38.5°C); 5) white blood cell (WBC) count ≥5 cells per high power field on centrifuged urine sediment or > 10^5 CFU/ml microorganisms in urine culture.[7] Infected site (right, left, and both) was localized with clinical symptoms such as flank pain and costovertebral angle tenderness. In cases with vague clinical symptoms, we judged the localization by radiologic findings. The urine collecting methods for males were that lift the prepuce, wash the urethral meatus and collect the mid-stream urine in a sterile plastic cup with a lid, and in female cases, wash the perineum and the urethral meatus by the identical method, and collect the mid-stream urine.

For urine culture, all patients were advised to collect a clean-catch midstream urine sample in a sterile wide-mouthed container supplied by the laboratory and to bring the sample to the laboratory as early as possible. Identification of bacterial pathogens was made by microscopy, culture, and conventional biochemical tests. Antibiotic susceptibility testing will be done for ceftriaxone, cefixime, ceftazidime, cefepime, imipenem, meropenem, azithromycin, co-trimoxazole, moxifloxacin, linezolid, tigecycline, cefuroxime, gentamicin, ciprofloxacin, levofloxacin, doxycycline, nitrofurantoin, amikacin, piperacillin-tazobactam, and co-amoxiclav. The presence of renal failure, need for dialysis, and hospital stay will be recorded as outcome variables.

Comparison of continuous variables between independent two groups was performed by t-test, comparison of the frequency was analyzed by Pearson chi-square test, and the criterion of the determination of significance was $p<0.05$. Data were analyzed by SPSS software.

Results

Among the total 100 cases, 51 cases were male, 49 cases were female, and the ratio of male to female was 1.04:1. The mean age was 48.60 ± 12.28 yrs. Most of our patients (88%) were between 30 to 69 years of age, and the highest frequency (35%) was observed in the 50 to 59 years age group. The mean duration of hypertension was 8.63 ± 4.64 years, and the mean duration of diabetes was 7.98 ± 4.51 years. Mean hospital stay was 5.70 ± 1.20 days. The mean total count of WBC, serum creatinine, and RBS were 15534.0 ± 3356.71, 4.53 ± 4.76, and 9.96 ± 6.81, respectively. The mean total sensitive antibiotic was 4.69 ± 2.37, and total resistant antibiotic was 8.60 ± 2.70 respectively [Table-1 & Figure- I].

Table 1: Mean (± SD) values of sociodemographic and clinical characteristics (N=100)

Variables	Mean ± SD.
Age (years)	48.60 ± 12.28
Duration of diabetes (years)	7.98 ± 4.51
Duration of hypertension (years)	8.63 ± 4.64
Hospital stay (days)	5.70 ± 1.20
Total count of WBC (/cmm)	15534.0 ± 3356.71
Serum creatinine (mg/dl)	4.53 ± 4.76
RBS (mg/dl)	9.96 ± 6.81
Total sensitive antibiotic	4.69 ± 2.37
Total resistant antibiotic	8.60 ± 2.70

The age group included in this study ranged between 15 to 80 years. The maximum numbers of patients were in the age group of 50-59 years (35.0%) [Figure-I].

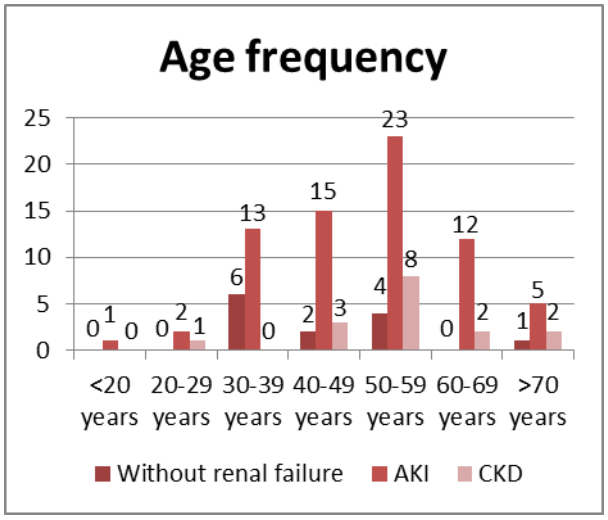

Figure-I: Age distribution of patients with APN

Out of these 100 patients, 87% patients had renal failure; among them, 81.6% had AKI, and 18.4% were suffering from CKD. Leukocytosis was present in 82% of patients. Among patients without renal failure, 61.5% of patients had >30 pus cells in the urine, and only 7.7% of patients had BOO. 97.2% of patients with AKI had leukocytosis, 67.6% patients had >30 urinary pus cells, and 16.9% patients had BOO. Among patients with CKD, none had leukocytosis;> 30 pus cells in urine were present in 50% of patients, and BOO was present in 18.8% of patients [Table-2].

E. coli was isolated in 88 (88%) patients; *Pseudomonas* in 9 (9%) patients and *Klebsiella* were isolated in 3 (3%) patients as a causative organism for APN. Most of the patients with APN were >30 Years of age (96.0%). DM was present in 50.0%, and hypertension was present in 30.0% of patients. 19.0% of patients had a history of diabetes for more than ten years, and 28.0% of patients had a history of hypertension for more than five years. There was no significant difference of bacterial isolates in different age groups, sex groups, patients with DM, and DM duration more than ten years. In both males and females, *E. coli* was the major causative bacteria (51.1% vs. 48.9%). *Klebsiella* infection was significantly more frequent among CKD patients (66.7%, $p<0.05$) [Table-3].

Commonly used antibiotics like ceftriaxone were found significantly resistant in the case of *E. coli* ($p<0.01$) and *klebsiella* ($p<0.05$). Most bacterial isolates were found to be resistant to many other antibiotics that are commonly used in UTI in our countries, such as cefixime, cefuroxime, co-amoxiclav, and co-trimoxazole. In the majority of cases (>50%), *E. coli* was susceptible to nitrofurantoin, amikacin, imipenem, meropenem, and piperacillin-tazobactam. *pseudomonas* was susceptible to meropenem, imipenem, amikacin, levofloxacin. It is also significantly susceptible to ceftazidime ($p<0.05$) ciprofloxacin and cefepime ($p<0.01$) [Table-4.b]. E. Coli is also significantly sensitive to tigecycline ($p<0.05$) [Table-4.a]. In most cases *pseudomonas* was susceptible to meropenem, imipenem, amikacin, levofloxacin. It is also significantly susceptible to ceftazidime ($p<0.05$) ciprofloxacin and cefepime ($p<0.01$) [Table-4.b]. Most of the Klebsiella were found to be susceptible to meropenem, levofloxacin, amikacin, and nitrofurantoin [Table-4.c,d].

Table 2: Investigations profile of patients with APN. (N=100)

	Without renal failure (n=13) n (%)	**With renal failure AKI (n=71) n (%)**	**CKD (n=16) n (%)**
TC (WBC) >11,000/ cmm	13 (100)	69 (97.2)	0 (0)
Urine albumin			
Trace	0 (0)	5 (7.0)	3 (18.8)
+	10 (76.9)	41(57.8)	8 (50.0)
++	3 (23.1)	24 (33.8)	4 (25.0)
+++	0 (0)	1 (1.4)	1 (6.2)
Urine pus cell			
<10	0 (0)	7 (9.9)	1 (6.2)
10-20	3 (23.1)	12 (16.9)	5 (31.3)
20-30	2 (15.4)	4 (5.6)	2 (12.5)
>30	8 (61.5)	48 (67.6)	8 (50.0)
Urine RBC			
<5	8 (61.5)	34 (47.9)	11 (68.8)
5-10	4 (30.8)	31 (43.7)	4 (25.0)
10-20	0 (0)	3 (4.2)	0 (0)
>20	1 (7.7)	3 (4.2)	1 (6.2)
Renal stone	0 (0)	2 (2.8)	0 (0)
BOO	1 (7.7)	12 (16.9)	3 (18.8)

NB- WBC- white cell count.
BOO- bladder outlet obstruction.

Table 3: Sociodemographic characteristics of the patients and their relationship with types of bacteria isolated from urine culture (N=100)

		E. coli	***Pseudomonas***	***Klebsiella***
		(n=88)	(n=9)	(n=3)
		n (%)	n (%)	n (%)
Age	<30	4 (4.5)	0 (0)	0 (0)
	>30	84 (95.5)	9 (100)	3 (100)
Sex	Male	45 (51.1)	5 (55.6)	1 (33.3)
	Female	43 (48.9)	4 (44.4)	2 (66.7)
DM		44 (50.0)	4 (44.4)	2 (66.7)
	Duration >10 years	17 (38.6)	1 (25.0)	1 (50.0)
Hypertension		26 (29.5)	3 (33.3)	1 (33.3)
	Duration >5 years	25 (96.2)	2 (66.7)	1 (100)
Renal failure		75 (85.2)	9 (100)	3 (100)
	AKI	63 (84.0)	7 (77.8)	1 (33.3)
	CKD	12 (16.0)	2 (22.2)	2 (66.7)*****
Total		88 (100)	9 (100)	3 (100)

*p<0.05, **p<0.01

Table 4: Susceptibility of bacteria to various drugs (N=100)

Table 4 (a): Susceptibility of bacteria to Cephalosporins and Penicillins.

Cephalosporines and penicillins	**Ceftriaxone n (%)**	**Cefixime n (%)**	**Ceftazidime n (%)**	**Cefepime n (%)**	**Cefuroxime n (%)**	**Co-Amoxiclav n (%)**
***E. coli* (n=88)**	**			*		
Sensitive	2 (2.3)	4 (5.1)	10 (13.3)	7 (9.5)	7 (8.2)	6 (22.2)
Resistant	85 (97.7)	75 (94.9)	65 (86.7)	67 (90.5)	78 (91.8)	21 (77.8)
Total	87 (100)	79 (100)	75 (100)	74 (100)	85 (100)	27 (100)
***Pseudomonas* (n=9)**			*	**		
Sensitive	1 (16.7)	0 (0)	4 (44.4)	4 (44.4)	0 (0)	1 (33.3)
Resistant	5 (83.3)	4 (100)	5 (55.6)	5 (55.6)	6 (100)	2 (66.7)
Total	6 (100)	4 (100)	9 (100)	9 (100)	6 (100)	3 (100)
***Klebsiell*a (n=3)**	*					
Sensitive	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Resistant	2 (66.7)	3 (100)	3 (100)	3 (100)	3 (100)	2 (100)
Total	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)	2 (100)
Total (n=100)	*					
Sensitive	4 (4.2)	4 (4.7)	14 (16.1)	11 (12.8)	7 (7.4)	7 (21.9)
Resistant	92 (95.8)	82 (95.3)	73 (83.9)	75 (87.2)	87 (92.6)	25 (78.1)
Total	96 (100)	86 (100)	87 (100)	86 (100)	94 (100)	32 (100)

*- Significant ($p<0.05$), **- Significant ($p<0.01$).

Table 4 (b): Susceptibility of bacteria to quinolones.

Quinolones	Moxifloxacin n (%)	Ciprofloxacin n (%)	Levofloxacin n (%)
***E. coli* (n=88)**		*	*
Sensitive	2 (4.9)	20 (23.3)	23 (30.3)
Resistant	39 (95.1)	66 (76.7)	53 (69.7)
Total	41 (100)	86 (100)	76 (100)
***Pseudomonas* (n=9)**		**	
Sensitive	0 (0)	6 (66.7)	5 (62.5)
Resistant	6 (100)	3 (33.3)	3 (37.5)
Total	6 (100)	9 (100)	8 (100)
***Klebsiell*a (n=3)**			
Sensitive	0 (0)	1 (33.3)	2 (66.7)
Resistant	2 (100)	2 (66.7)	1 (33.3)
Total	2 (100)	3 (100)	3 (100)
Total (n=100)			
Sensitive	2 (4.3)	27 (27.6)	30 (34.5)
Resistant	47 (95.7)	71 (72.4)	57 (65.5)
Total	2 (100)	98 (100)	87 (100)

*- Significant ($p<0.05$), **- Significant ($p<0.01$).

Table 4 (c): Susceptibility of bacteria to other antibiotics

Others (a)	Imipenem	Meropenem	Piperacillin-tazobactum	Tigecycline	Linezolid	Amikacin
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
***E. coli* (n=88)**				*		
Sensitive	66 (86.8)	56 (93.3)	15 (88.2)	10 (71.4)	0 (0)	38 (70.4)
Resistant	10 (13.2)	4 (6.7)	2 (11.8)	4 (28.6)	9 (100)	16 (29.6)
Total	76 (100)	60 (100)	16 (100)	14 (100)	9 (100)	54 (100)
***Pseudomonas* (n=9)**				*		
Sensitive	7 (100)	5 (83.3)	3 (100)	0 (0)	0 (0)	5 (83.3)
Resistant	0 (0)	1 (16.7)	0 (0)	4 (100)	1 (100)	1 (16.7)
Total	7 (100)	6 (100)	3 (100)	4 (100)	1 (100)	6 (100)
***Klebsiell*a (n=3)**						
Sensitive	1 (100)	3 (100)	-	-	-	2 (66.7)
Resistant	0 (0)	0 (0)	-	-	-	1 (33.3)
Total	1 (100)	3 (100)	-	-	-	3 (100)
Total (n=100)						
Sensitive	74 (88.1)	64 (92.8)	18 (90.0)	10 (55.6)	0 (0)	45 (71.4)
Resistant	10 (11.9)	5 (7.2)	2 (10.0)	8 (44.4)	10 (100)	18 (28.6)
Total	84 (100)	69 (100)	20 (100)	18 (100)	10 (100)	63 (100)

*- Significant ($p<0.05$), **- Significant ($p<0.01$).

Table-4 (d): Susceptibility of bacteria to other antibiotics

Others (b)	Azithromycin	Co-trimoxazole	Gentamycin	Doxycycline	Nitrofurantoin
	n (%)	n (%)	n (%)	n (%)	n (%)
E. coli (n=88)					
Sensitive	17 (38.6)	18 (29.0)	35 (48.6)	24 (41.4)	45 (57.0)
Resistant	27 (61.4)	44 (71.0)	37 (51.4)	34 (58.6)	34 (43.0)
Total	44 (100)	62 (100)	72 (100)	58 (100)	79 (100)
***Pseudomonas* (n=9)**					
Sensitive	1 (33.3)	0 (0)	4 (44.4)	-	4 (66.7)
Resistant	2 (66.7)	8 (100)	5 (55.6)	-	2 (33.3)
Total	3 (100)	8 (100)	9 (100)	-	6 (100)
***Klebsiell*a (n=3)**					
Sensitive	0 (0)	1 (50.0)	1 (33.3)	0 (0)	2 (66.7)
Resistant	1 (100)	1 (50.0)	2 (66.7)	2 (100)	1 (33.3)
Total	1 (100)	2 (100)	3 (100)	2 (100)	3 (100)
Total (n=100)					
Sensitive	18 (37.5)	19 (26.4)	40 (47.6)	24 (38.7)	51 (58.0)
Resistant	30 (62.5)	53 (73.6)	44 (52.4)	38 (61.3)	37 (42.0)
Total	48 (100)	72 (100)	84 (100)	62 (100)	88 (100)

*- Significant ($p<0.05$), **- Significant ($p<0.01$)

Discussion

UTI is a bacterial infection that can be encountered frequently in clinics, and APN is the most severe form of UTI. In our study, the mean age was 48.60 (±12.28) years which is somewhat lower than Jang 2019 and Jeon 2019, but the age range was similar to our study.[13,14] Depending on reports, the ratio of male to female varies from 1:7 to 1:13.1 [8–10], and in our study prevalence of APN in male and female are almost equal. Diabetes was present in 50.0% of patients. The frequency of DM was very high in our patients as compared to other studies, which are around 25%.[13] As our study was done among hospitalized patients and diabetic patients are more prone to develop complications of APN like septicemia and renal failure requiring hospitalization. So, the frequency of DM in hospitalized patients may be higher. Around 87% of patients developed renal failure in our study. Among them 81.6% (n=71) had AKI and 18.4% (n=16) had CKD. The frequency of renal failure both AKI and CKD among hospitalized patients was found to be higher compared to other studies.[13,14]

In our study, the total count of WBC was higher as compared to Jeon 2019. As the frequency of renal failure (mainly AKI) is higher in hospitalized patients recruited in our study, mean serum

creatinine (4.59 ±4.69 mg/dl) was also very high in our study as compared to Jeon et al.[14] High leukocyte count and high serum creatinine may be due to the reason that patients without septicemia or renal failure are less likely to be admitted in a resource-poor setting like RMCH. As for causative microorganisms, *E. coli* accounted for 83% and is in agreement with previous reports.[15,16,17]

The rate of antibiotic resistance is high among uropathogens. The frequency of resistance to antibiotics is directly linked to irrational use of antibiotics and also inadequate dose and duration. Treatment of UTI is often started empirically, and therapy is based on information determined from the antimicrobial sensitivity pattern of the urinary tract pathogens in a given community.[11,12] Now a day's more and more drug-resistant strains of uropathogens have been isolated in patients with APN admitted to hospital than before. Ongoing research on the susceptibility pattern of uropathogens is necessary for the precise choice of empirical antibiotic therapy.

In other countries, it has been reported that antibiotic sensitivity for co-trimoxazole was 67-83.2%, 78-98.1% for ciprofloxacin, and 25-82.3% for ampicillin.[18–20] In South Asia, Min et al. reported that antibiotic sensitivity for ampicillin was 13.2%, to co-trimoxazole 44.7%, to ciprofloxacin 86.5%, and to amikacin 98.3%. According to our study and previous studies reported in Bangladesh, we found that the antibiotic resistance to co-trimoxazole is higher than that of western countries.[17] In this study, sensitivity to co-trimoxazole, amikacin, and ciprofloxacin was 23.3%, 69.8%, and 26.0%, respectively. Overall sensitivity to nitrofurantoin was 57%. The high sensitivity of E.coli for fluoroquinolones was observed by Shalini et al. [21] and other studies [22,23], but it was low for ciprofloxacin (27.6%), levofloxacin (34.5%), and moxifloxacin (4.1%) in our study. Jang et al. also found low sensitivity to fluoroquinolone (23%) and co-trimoxazole (32%). The study has shown low sensitivity to aminoglycoside (21%), but in our study, increasing sensitivity to less-used antibiotics such as gentamicin (47.6%) and doxycycline (40.0%) was observed.[13] Poor sensitivity of all types of uropathogens were observed to cephalosporins (4.2-16.1%), and this finding is consistent with other studies (15%). In most cases, *E. coli* was found to be sensitive to meropenem, imipenem, piperacillin-tazobactam, nitrofurantoin, and amikacin. In comparison, *pseudomonas* was found to be sensitive to ciprofloxacin, gentamycin, ceftazidime, and cefepime. Overall, 95.8% of bacterial isolates were found to be resistant to ceftriaxone, 95.3% to cefixime, 83.9% to ceftazidime, 87.2% to cefepime, and 92.6% to cefuroxime. Other antibiotics against which more resistance was observed are- moxifloxacin (95.7%) and linezolid (100%).

Conclusion

Resistance to antibiotics shows a trend on the rise; hence, antibiotic stewardship is required. Particularly, antibiotics resistance to cephalosporines is high, and the sensitivity is on the decrease with time. Therefore, their selection as first-line drugs should be reconsidered.

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