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Urinary Tract Infection due to Extended-Spectrum Beta-Lactamase Producing Organisms is a Risk Factor for Acute Kidney Injury among Patients with Type 2 Diabetes Mellitus

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Abstract:

Background: *Urinary tract infection (UTI) is common and diabetic patients are at increased risk for UTI. UTI may be complicated by acute kidney injury (AKI). This study was designed to evaluate whether UTI due to extend ed-spectrum beta-lactamase (ESBL) producing organisms should be considered as a risk factor for AKI in type 2 diabetic subjects.*

Methods: *This case-control study was done in a tertiary care hospital in Dhaka, Bangladesh from April to June 2016. Type 2 diabetic subjects with culture proven UTI were evaluated. Patients with UTI complicated by AKI were cases and those without AKI were taken as controls. ESBL-positivity of the isolated organisms was evaluated as risk factor for AKI.*

Results: *During the study period, a total of 131 (male to female ratio 1:2.6) type 2 diabetic subjects with culture proven UTI were enrolled. Mean age and mean duration of diabetes were 56.1±13.3 and 8.7±5.4 years respectively. Escherichia coli (82, 62.6%) was the commonest aetiological agent followed by Klebsiella pneumoniae(14, 10.7%). Two-thirds (55/82, 67.1%) of E. coli and two-fifths (6/14, 42.9%) of Klebsiellae were ESBL-positive. UTI in 64 (48.9%) patients were due to ESBL-positive organisms. Out of 131 UTI patients, 62 (47.3%) had AKI; 40 (40/64, 62.5%) among ESBL-positive and 22 (22/67, 32.8%) among non-ESBL organisms. There were no significant difference in relation to age (p=0.71), sex (p=0.26), duration of diabetes (p=0.37) and glycated haemoglobin (HbA1c) (p=0.69) between cases and controls. ESBL-positivity appeared as a significant risk factor for AKI among the study subjects (OR=3.4, 95% CI=1.66-6.99, p=0.008).*

Conclusions: *Almost half of the type 2 diabetic subjects with UTI had ESBL-positive organisms as aetiological agents in this study. UTI due to ESBL-positive organisms was a significant risk factor for AKI.*

Key words: *Acute kidney injury, extended-spectrum beta-lactamase, risk factor, type 2 diabetes mellitus, urinary tract infection.*

Introduction:

Urinary tract infection (UTI) is one of the most common bacterial infections in adults. Female patients and patients with diabetes mellitusare at increased risk for UTI.[1,2] Escherichia coli and Klebsiella pneumoniae are the two most common organisms responsible for UTI throughout the world.[3-6] Extended-spectrum beta-lactamase (ESBL) producing strains are an ever increasing problem[7-9] and diabetic patients with long duration and poor glycaemic control are at increased risk for UTI due to ESBL-positive organisms.[5,10] UTI may be complicated by acute kidney injury (AKI) and sepsis.[3] This study was designed to evaluate whether UTI due to ESBL-positive organisms should be considered as a risk factor for AKI in type 2 diabetic subjects.

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Methods:

This case-control study was done in the Department of Internal Medicine and Department of Nephrology of Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General Hospital, Dhaka, Bangladesh from April to June 2016. Hospitalized patients with a clinical diagnosis of UTI were initially enrolled for the study purpose. A clean catch technique was applied for urine (preferably early morning midstream specimen) collection.

Collected samples were sent to the microbiology laboratory within half an hour, where these samples were inoculated within two hours in Mac Conkey agar and blood agar. Significant culture positive cases (semi-quantitative colony count >$1x10^5$ colony forming units/ml) were then included for the study purpose. Catheterized patients, pregnant ladies, patients with inadequate/no growth or growth of candida on urine culture were excluded from the study. Growth of organisms was further evaluated by their colony characters and biochemical tests including triple sugar iron (TSI), motility indole urea (MIU) and Simon citrate. Then the selected samples were sub-cultured for antibiotic sensitivity in Muellar-Hilton (MH) agar by Kibry-Bauer disc susceptibility test.[11] ESBL-positivity was determined phenotypically by Double Disc Synergy Test. Besides the urine culture, patients were evaluated clinically and by other required laboratory tests. Whether patients developed AKI was noted. AKI was diagnosed as per Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline 2012.[12] Then, patients with UTI complicated by AKI were taken as cases and UTI cases without AKI were controls. Finally, ESBL-positive organisms were evaluated as risk factor for AKI among the study participants. Statistical package for social sciences (SPSS) version 20.0 was used to analyze data. A p value of <0.05 was taken as significant. Results were presented in tables.

Results:

During the study period, a total of 131 type 2 diabetic subjects,including 95 females, with culture proven UTI were enrolled. Mean age and mean duration of diabetes of the study participants were 56.07±13.30 and 8.70±5.39 years respectively. Sixty two (47.3%) patients with UTI were complicated by AKI (cases). There was no significant difference regarding age, sex, duration and control of diabetes between cases and controls (Table I). E. coli (82, 62.6%) was the commonest aetiological agent followed by Klebsiellae (14, 10.7%). Two-thirds (55/82, 67.1%) of E. coli and two-fifths (6/14, 42.9%) of Klebsiellae were ESBL-positive (Table II).

Table-I

Base-line characteristics of the study subjects (N=131)

Characteristics	Overall (N=131)	Cases (UTI with AKI) (n=62)	Controls (UTI without AKI) (n=69)	p value
Mean age (years)	56.07±13.30	55.61±14.13	56.48±12.59	0.7100
Male:Female	1:2.64	20:42	16:53	0.2460
Mean duration of DM (years)	8.70±5.39	9.15±5.40	8.30±5.39	0.3696
Mean HbA1c (%)	8.93±1.96	9.0±1.78	8.86±2.13	0.6857

Table-II

Aetiological agents among the study subjects (N=131)

Bacteria	ESBL-positive	Non-ESBL	Total
E. coli	55 (42.0)	27 (20.6)	82 (62.6)
K. pneumoniae	6 (4.6)	8 (6.1)	14 (10.7)
Pseudomonas spp.	---	3 (2.3)	3 (2.3)
Citrobacter	---	3 (2.3)	3 (2.3)
Staphylococcus	---	7 (5.3)	7 (5.3)
*MRSA Staph	---	1 (0.8)	1 (0.8)
Enterococcus	---	10 (7.6)	10 (7.6)
Acinetobacter	---	6 (4.6)	6 (4.6)
Citrobacter	1 (0.8)	---	1 (0.8)
Streptococcus	---	2 (1.5)	2 (1.5)
Enterobacter	2 (1.5)	---	2 (1.5)
Total	64 (48.9)	67 (51.1)	131 (100)

*MRSA = Methicillin resistant Staphylococcus aureus

UTI in 64 (48.9%) patients were due to ESBL positive organisms. Out of 131 UTI patients, 62 (47.3%) had AKI; 40 (40/64, 62.5%) among ESBL-positive and 22 (22/67, 32.8%) among non-ESBL organisms. ESBL-positivity appeared as a significant risk factor for AKI among the study subjects (Table III).

Table-III

Evaluation of UTI with ESBL-positive organisms as risk-factor for AKI among the study subjects (N=131)

Bacteria	ESBL positive	Non ESBL	Total
ESBL-positive (64)	40	24	3.4,
Non-ESBL (67)	22	45	1.66-6.99, 0.008

Discussion:

The definition of AKI has evolved through different stages and KDIGO defined AKI as having one or more of following 3 criteria: absolute rise of serum creatinine value more than 0.3 mg/dl in a 48-hour period, a rise of serum creatinine to 1.5 times of base-line in one week and decrease in urine production to less than 0.5 ml/kg/hour for more than 6 hours.[12] This is the most updated and widely used criteria for AKI and we used this definition in our study to define AKI. We relied mostly on first two criteria based on serum creatinine values.

AKI is common in hospital settings and more common in intensive care units (ICU).[13] Patients with diabetes are also at increased risk for AKI.[14] Past history of AKI and CKD are reported risk factors for AKI.[14] UTI may be complicated by AKI.[3,15] Older age, diabetes, upper UTI, poor base-line renal functions are reported risk factors for AKI in UTI.[15]

In our study, we evaluated ESBL-positivity of organisms causing UTI as risk factor for AKI. UTI due to ESBL-positive organisms are increasingly been reported in Bangladesh[16-18] and Rahim MA et al[10] reported that diabetic females with long duration and poor glycaemic control are risk factors for UTI due to ESBL-positive organisms. Similar observation was reported in other studies.[5,19-22] Prior hospitalization and repeated UTI and antibiotic intake were risk factors for UTI due to ESBL-positive organisms in another study.[23] UTI due to ESBL-positive organisms can deteriorate kidney function in kidney transplant recipients as well.[24] We found ESBL-positivity as a significant risk factor for AKI in patients with type 2 diabetes mellitus.

This study had some potential limitations. It was a single center study, the study period was only 3 months and the sample size was small. We did not evaluate other risk factors for AKI like base-line kidney function, concomitant treatment with angiotensin blocking agents i.e. angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), hydration status of patients as vomiting is a common feature in UTI[4] and whether patients were treated with any antibiotic with nephrotoxic potential like aminoglycoisdes. Taking all these confounders in considerations, a larger, multicenter study will give a more reliable answer to the research question tested in this study. Diabetic patients with UTI complicated by AKI merit long-term follow up for their ultimate renal outcomes,[25] consideration of this fact was also beyond our capacity in this particular study.

Conclusions:

In conclusion, it can be said that UTI due to ESBL-positive organisms are increasing; almost half of the type 2 diabetic subjects had UTI due to ESBL-positive agents in this study. UTI due to ESBL-positive uropathogens appeared as significant risk factor for AKI among patients with type 2 diabetes. A good glycaemic control and general measures to prevent UTI may become helpful in prevention of UTI due to ESBL-positive organisms and thus may reduce the risk of AKI among type 2 diabetic patients.

Conflict of interest: None.

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