LET'S EXPLORE: PREDICTIVE ABILITY OF URINALYSIS FOR DIAGNOSIS OF URINARY TRACT INFECTION IN CKD PATIENTS

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Abstract

Background: Immuno-compromised Chronic Kidney Disease (CKD) patients are more vulnerable to infection. Among all infections, Urinary Tract Infection (UTI) is the main culprit of increased morbidity and mortality. So to combat this and to retard disease progression, control of UTI is a prime concern for this group of patients. Quantitative urine culture is the 'gold standard' method for definitive diagnosis of urinary-tract infections, but it is intensively time and labor consuming. For initiating early empirical treatment even in absence of localizing symptoms, the same day result is very helpful. Culture may lead to delaying of diagnosis. The microscopy of urine thus may be an essential tool for the diagnosis of patients with urinary tract infections. The aim of this study was to evaluate the diagnostic performance of the common urinalysis parameters in comparison to urine culture as the reference method.

Materials and methods: We evaluated 1000 urine samples, submitted for urine analysis and culture admitted in Nephrology ward, Chattogram Medical College Hospital, a large tertiary care hospital for one year from 1st January 2017 to 31st December 2017. A cross-sectional study was done. Different Cut-off values were determined from different studies obtained by comparing the results with urine cultures. The test characteristics by the sensitivity, specificity, PPV and NPV were calculated for bacteria and White Blood Cells (WBCs) Red Blood Cells (RBC) glucose in urine and albuminuria. A practical diagnostic threshold of bacteriuria was determined. The diagnostic performance of culture was compared with different parameters of urinalysis.

Results: Among the 1000 urine specimens submitted for culture, 618 cultures (61.8%) were positive, and 382 were (38.2%) negative. The cut-off value for pyuria was determined ≥10 pus cell/HPF and compared for bacteriuria (Sensitivity: 69%, specificity: 36%, PPV: 64%, NPV: 42%) and presence of sugar and albumin in urine were found associated significantly with culture positivity at 95% CI (Sensitivity: 15%, specificity: 90%, PPV: 70%, NPP: 39% and sensitivity: 97%, specificity: 6%, PPV: 62%, NPP: 59%) respectively. And association between RBC and pus cell in urine microscopy was significant.

Conclusions: UTI is a common infection in CKD patients with high incidence. Though culture is the gold standard, but urinalysis by cell count for pyuria, dipsticks for the presence of sugar or albumin may be helpful to diagnose UTI. The association of these all characteristics with growth in culture was statistically significant.

Key words

CKD; UTI; Urinalysis; Growth of organisms in culture.

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Introduction

The prevalence of UTI is 28 to 83 percent, based on a reference standard of 10^5 Colony Forming Units (CFU) per ml on urine culture[1]. Among general population two third of patients have symptoms when age more than 14 years[2]. Three symptoms (Dysuria, urgency and nocturia) had a positive Likelihood Ratio (LR) significantly greater than 1.0 (1.1, 1.2 and 1.3, respectively). Dipstick urinalysis is more accurate than any individual symptom[3-5]. Again diagnostic value of pyuria and association of glucose and protein in urine is studied several times for rapid diagnostic tool comparing the gold standard. There are different studies

that had debate with variable Sensitivity (Se) Specificity(Sp) Positive Predictive Value (PPV) Negative Predictive Value (NPV) of all these parameters. Moreover patients of CKD especially Dialysis patients who are more susceptible to (UTI) are with increased risk of morbidity and mortality[6-8]. Delayed diagnosis is an important issue in this group especially because UTI symptoms are reduced or absent in these patients due to different mechanisms. When early diagnosis is possible in a faster time, these infections are easily treatable[9]. So the question is often raised whether urinalysis especially pyuria, glucose or protein in urine is predictive of UTI in CKD patients when early treatment is attempted. But the role is uncertain till date[9-11]. The sensitivity and specificity of pyuria is variable with a excessive variability of 11-70%[12-15]. So this study was aimed to evaluate the diagnostic accuracy of the common urinalysis parameters in comparison to urine culture as the reference method.

Materials and methods
This cross-sectional study was conducted by reviewing the records for all patients of CKD admitted to Nephrology ward over the period from 1 January 2017 to 31 December 2017. The patients having CKD and fulfilled the inclusion criteria i.e. every subject of both sex aged >18 years with or without dialysis were included consecutively. They were requested to participate in the study and subsequently recruited on giving consent voluntarily. They were selected irrespective of symptoms of UTI. CKD patients with pyuria getting antibiotic for more than 48 hours before admission or any other immunosuppresives and patients with anuria (As urine for collection was not available), pregnancy and who did not provide written consent were excluded. A pre-formed standard case record form was used for data collection. All of the medical records of the patients were reviewed and determined the stage of CKD. A second midstream clean-catch urine sample at least >20 ml was collected in the clean, sterile, dry container by standard procedure Examination and culture of urine: Urine samples were tested by using multiple reagent strips and microscopic urinalysis. A urine dipstick consists of chemically treated paper, which displays different colors indicating the presence of sugar, protein, specific gravity and pH. The cut-off value for pyuria was determined >10pus cell/HPF by cell count method and detection thresholds were set by qualitative presence or absence for sugar and albumin in urine.

All samples were inoculated on Blood agar and MacConkey agar by the semi-quantatitive culture technique using a standard wire loop and incubated at 37℃ for 24-48 hours in an incubator. The approximate number of colonies and the number of bacteria was counted. Bacteriuria was defined as any micro-organisms growth of $\geq 10^5$ CFU/ml or $\geq 10^3$ CFU/ml in symptomatic patients. The isolated organisms were identified by standard biochemical method which involves morphological appearance of the colonies, staining reactions and biochemical properties[16].

Ethical Committee approval was duly obtained from the Institutional Review Board of Chattogram Medical College Hospital, Chattogram prior commencement of the study.

Data were collected by interview & recording reports of laboratory investigations. All the collected data were checked and verified. The data were compiled, analyzed and then tabulated according to key variables. The data were entered into computer statistical analysis of the results and analyzed by using qualified windows based computer (SPSS for windows 20, SPSS in C Chicago (IL,USA). All data were evaluated by using necessary statistical methods-Chi-square test for categorical variables and t-test for continuous variables. Sensitivity, specificity, PPV, NPV was used to assess the diagnostic performance of variables comparing gold standard. The results were presented in tables and figures. Mean for numerical variables and percentage for categorical variables was used as statistical term in this study. Statistical significance was set at p<0.05 and confidence interval was set at 95% level.

Results
In this study with 1000 patients ,the mean age was 48.5±14.75 years and female was more with UTI and sex distribution was significant. Aetiology of CKD also influenced on UTI in study population and UTI was more associated with higher CKD stages significantly.

Table I : Association between pyuria and growth of organisms.

Urinary	pus cell/HPF growth of organisms				Total		p value
	Yes –n	%	No –n	%	n	%	
< 10 cell	187	57.4	139	42.6	326	32.6	0.042*
≥10cell	431	64.0	242	36.0	673	67.7	

Data are presented as frequency (n) and percentage (%).

*Significant in Chi-square test.

Association between type of organism and urine pus cell p=0.744†

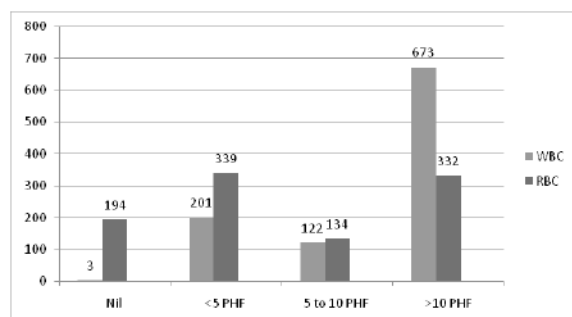(Not significant in Chi-square test: Not shown).

Fig 1 : Association between RBC & pus cell count in urine microscopy (p<0.001).

Table II: Association between urine sugar and growth of organisms.

Urine sugar	Growth of organisms					Total		p value
	Yes- n	%	No –n	%		n	%	
Nil	534	60.6	347	39.4		881	88.1	0.036*
Present	84	70.6	35	29.4		119	11.9	

Data are presented as frequency (n) and percentage (%).

* Significant in Chi-square test

* Association between type of organism and urine albumin p=0.119 (Not shown).

Table III: Association between proteinuria and Growth and type of organisms.

Urine albumin	Growth of organisms				p value
	Yes-n	%	No-n	%	
Nil	15	40.5	22	59.5	
Trace	88	66.2	45	33.8	
1+	284	68.8	129	31.2	<0.001*
2+	188	61.4	118	38.6	
3+	43	38.7	68	61.3	

*Association between proteinuria and Growth is significant.

Table IV: Diagnostic remarks for urinalysis predicting UTI in CKD patients (n=1000).

Predictors	Cut-off value	SEN%	SPE%	PPV%	NPV%
Pyuria	≥10puscell/HPF	69	36	64	42
Sugar	Glucose present	15	90	70	39
Albumin	Trace or more	97	5.7	62	59

Discussion

Out of 1000 urine samples, total 618(61.8%) were found to be culture positive, whereas 382 (38.20%) were found to be culture negative. The prevalence of bacteriuria among male was found to be 54.2% n=225 and female 67.2% n=393. The incidence of bacteriuria was highest ie.23.3% in the age group of (51-60) years. A similar study done by Golebiewska et al showed a higher positive growth rate of 65%[17]. But this study did not find similarity with the recent study conducted in western Nepal by Jaiswal et al with culture positivity rate 30%[18]. The reason behind this variable range of may be slow growing organism or fastidious organism, different treatment pattern by patients or variation in patients biochemical and immune status . Renko et al suggested that this occurs more with low GFR significantly which is consistant with our study[19].

Out of 618 culture positive patients, significant pyuric group (Pus cell ≥ 10) had 67% UTI but the group with pyuria (Pus cell<10) showed 32.6% UTI. And association between urinary pus cell and growth was p =0.042. Our study was in agreement with the notion that higher the number of pus cell/HPF in urine, higher the culture positivity[1,9]. Pyuria was significantly more frequent in oliguric patient and those on HD which was also supported by Jaiswal et al[18]. But Study done by Eisinger and colleagues concluded that pyuria is not a good marker UTI in HD patients[20]. Recently Richa et al also assessed higher prevalence of UTI among patients with pyuria below cut-off value[21].

Pyuria is a marker of UTI even in asymptomatic UTI on HD. Falah et al reported that pyuria was a good marker for detection of UTI in 70% of culture positive cases[22]. LR Fasolo concluded that presence of pyuria in highly suggestive of UTI without renal failure. But in patients with renal failure coexistence of UTI with pyuria is highly variable (11-70%)[9]. Low urine volume, bladder stasis may be important factor leading high prevalence of pyuria in ESRD.

Some researchers remarked pyuria ≥10cells/HPF as cutoff value to diagnose UTI based on culture. Saitoh et al, Chaudry et al concluded that pyuria is a good marker of infection[13,14]. They reported Se 82%, Sp 99%, PPV 99%, NPV 87% and Se 88%, Sp 88%, PPV 70%, NPV 96% respectively. On the contrary, studies done by Eisenger et al & Orlowska et al raised an impression that pyuria

was not a good predictor of culture positivity[20,23]. They found Se 50%, Sp 69%, PPV 11%, NPV 95% and Se 67%, Sp 87%, PPV 67%, NPV 87% respectively. Our study evaluated pyuria with the same cutoff value with Se 69%, Sp 36%, PPV 64%, NPV 42%. Those studies included only HD patient while our study selected all stages of CKD.

Our study showed significant association of UTI with presence of glucose in urine p=0.004. Diabetic patients are prone to UTI due to the factors influencing host defense. Amy et al, stated, Hyperglycemia itself does not predictably increase rates of bacterial multiplication but elevated urinary or tissue glucose levels impair neutrophil function[24]. Asymptomatic urinary bacteriuria is particularly prevalent in diabetic patients with microalbuminuria[11]. No clear linear relationhip between glycosylated haemoglobin and UTI risk has been clarified. It is difficult to interpret data in either early or late stage patients because of the existence of albuminuria and functional proteiuria from urosepsis. Study done by Suresh et al in CKD patients found that with increase in urine sugar concentration, the chance of isolation of UTI-causing bacteria was significantly higher in diabetic patients[18].

Although UTI is often associated with albuminuria but the relationship is yet incompletely defined. Systematic review of infection in CKD, Macdonald stated that there is currently no evidence on the relationship between proteinuria and infection incidence independent of GFR. Our study revealed significant association between urinary albumin and growth of microorganism. Some reviews suggest 63-83% culture positive UTI having reagent strip test positive for protein[25]. High prevalence of association between proteinuria and asymptomatic UTI is reported in review by Joanne L. Carter et al[10]. UTI is to be excluded as this is a potential cause of proteiuria or a confounding factor. Whereas pre-existing proteinuria but not microalbuminuria is a risk factor of UTI. But by logistic regression analysis Van Nostrand et al showed proteinuria did not have a statistically significant independent relationship with presence of UTI (OR 1.29, p = 0.504) which is against our findings[26]. The high prevalence % of Albuminuria in our study may be even due to intrinsic renal disease rather than infection.

Limitations

- The study was for short duration and single centered.
- There was relative small sample size for subgroups of CKD which might distort the result of statistical analysis.
- All the lab investigations were not supported by single centre
- The predominant use of cell counts rather than hemocytometry may have introduced biases in the results of available studies.

Conclusion

UTI is a common infection in CKD patients with high incidence. Though culture is the gold standard, but urinalysis by cell count for pyuria, dipsticks for presence of sugar or albumin may be helpful to diagnose UTI. The association of these all characteristics with growth in culture was statistically significant.

Recommendation

- Large scale multicenter study should be done to get the national scenario
- A longitudinal follow up with multiple urinalysis for pyuria and culture to diagnose UTI may be applied
- Addition of nitrite and leukocyte esterase will increase the significance of urinalysis to diagnose UTI .

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Contribution of authors

MA: Conception, acquisition of data, interpretation of data, drafting, critical revision of content and final approval.

PKD: Interpritation of data critical revision of content and final approval.

GMTA: Conception, design, analysis, critical revision of content and final approval.

NH: Interpritation of data, critical revision and final approval.

RBK: Data acquisition & final approval.

SMI: Data acquisition, analysis, drafting and final approval.

Disclosure

All the authors declared no conflict of interest.

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