

Clinicolaboratory Profile and Outcome of Patients with Urosepsis at a Tertiary Care Centre in Southern India

HAGERA GULAM AHMED¹, GURAJALA SWATHI², ANUKOLU REDDY RAVISHANKAR³, HRV RAJ KUMAR⁴, LAKSHMI VEMU⁵

ABSTRACT

Introduction: Urosepsis is a serious, life-threatening consequence of a complicated Urinary Tract Infection (UTI). It is caused by bacterial infection of the urinary tract or prostate that spreads into the bloodstream. Since urosepsis is associated with a very high mortality rate (20-40%), an early diagnosis and identification of the causative bacteria is important so as to facilitate a prompt treatment with appropriate antibiotics. Nearly 50% cases of urosepsis are caused by the Gram Negative Bacterial (GNB) pathogen, *Escherichia coli* (*E. coli*).

Aim: To determine the bacteriological profile, antimicrobial susceptibility pattern, phenotypic resistance of the organisms associated with urosepsis and to correlate the levels of proinflammatory markers with the clinical outcome of the patient associated with urosepsis.

Materials and Methods: This was a prospective observational study including all patients with simultaneously positive urine

and blood cultures, with identical bacterial isolate(s). The details of clinical presentation, antibiotic therapy and other relevant information such as C-Reactive Protein (CRP) and Procalcitonin (PCT) values were recorded and analysed using Microsoft office excel 2013.

Results: *E. coli* was the commonest isolate (43/53, 81.1%). Of the total 43 *E. coli* isolates, 4/43 (9.3%) were Extended Spectrum Beta Lactamase (ESBL) producers and 23/43 (53.49%) were Carbapenemase producers. Significant rise of the proinflammatory markers (PCT>10 ng/mL) and (CRP>100 mg/l) were associated with high mortality (49%). Out of the 53 patients, 43.4% (23/53) patients had more than one risk factor associated with severe sepsis and poor prognosis.

Conclusion: Early recognition of symptoms followed by accurate diagnosis and early goal directed therapy is essential to decrease morbidity and mortality from urosepsis.

Keywords: Antibiotic susceptibility, Bacteriological profile, C-reactive protein, *E.coli*, Procalcitonin

INTRODUCTION

Urosepsis is defined as sepsis which is caused by infection of the urogenital tract and is a systemic response to infection. It is a life-threatening organ dysfunction caused due to a dysregulated host response to infection [1]. The signs and symptoms associated with Systemic Inflammatory Response Syndrome (SIRS) are now considered to be alerting symptoms which were initially considered to be “mandatory” for the diagnosis of sepsis [2,3]. “Sepsis” is a mosaic inflammatory response of the host to infection, often associated with a high mortality [4]. In about 30% of all septic patients, the infectious focus is localised in the urogenital tract [5]. The incidence of urosepsis increases with risk factors like age (≥ 65 years), diabetes mellitus, immune suppression (organ transplantation, chemotherapy, corticosteroid treatment, Acquired Immune Deficiency Syndrome (AIDS), nosocomial UTI and prior urological interventions [6,7].

Urosepsis must be detected at an early stage and promptly treated with appropriate antimicrobial agents to prevent complications [4]. The defining criteria for sepsis along with signs and symptoms of underlying cause of infection should be considered in the evaluation of sepsis. Urinalysis, urine culture and blood cultures must be performed in all patients with sepsis before antibiotic treatment is started [8]. Proinflammatory markers like PCT, CRP and Interleukin-6 (IL-6) also aid in the diagnosis of sepsis but the values should be interpreted in accordance with the cultures [9]. Outcome of the patients also depends on the infecting pathogen, early diagnosis and appropriate antibiotic therapy.

An early diagnosis and identification of the causative bacteria of urosepsis is important so as to facilitate a prompt treatment with appropriate antibiotics. In this study, the levels of proinflammatory markers in relation to mortality due to urosepsis have been

evaluated. The present study was conducted to determine the bacteriological profile, antimicrobial susceptibility pattern and the resistance phenotype of the organism causing urosepsis.

MATERIALS AND METHODS

A prospective observational study was conducted in the Microbiology Laboratory at Tertiary Care Hospital, for a period of two years from January 2018–December 2019. Institutional Ethical Clearance was obtained (KAMSRC/IEC/17/2017). Informed consent was obtained from the patients to use their clinical information for the study.

Urine specimen received from the patients, were inoculated by semi-quantitative method on chromogenic agar (CPSID, bioMerieux, France). The plates were incubated at 37°C for 24 hours. A growth of an isolate with more than 1 lac Colony Forming Units per milliliter ($>10^5$ CFU/mL) of urine was considered as significant bacteriuria [10]. Two sets FA plus (resin aerobic) and FN plus (resin anaerobic) of Bact/Alert blood cultures (bioMerieux, USA) were received from each patient. The bottles were loaded into BacT/Alert system and incubated at 37°C for five days. The samples flagged positive were unloaded from the system and subcultured on blood agar and chromogenic agar. The plates were incubated at 37°C for 24 hours. Any amount of growth of pathogenic bacteria on the plates was considered as significant [10].

All patients with simultaneously positive urine and blood cultures with an identical bacterial isolate were included in the study. Repeat isolates from the same patient were excluded from the study. The isolates were identified by VITEK 2 system (bioMerieux, France) using Identification cards for GNB (ID GN) (for GNBs) and Identification cards for GPC (ID GP) cards (for Gram Positive Cocci (GPCs) were used. Antimicrobial susceptibility testing was performed on the isolates on the VITEK2 system using the AST 628 (for GPCs) and AST 280 and

281 (for GNBs). The classes of antibiotics tested against GNB were Cephalosporins (3rd and 4th generation), Carbapenems, Polymyxins, Aminoglycosides, Quinolones and Beta lactam-Beta lactamase inhibitor combinations [11]. For GPCs, the antibiotic classes were Beta lactams, Aminoglycosides, Macrolides, Quinolones, Glycopeptides and Tetracyclines [11]. Multidrug resistance was documented in isolates showing resistance to more than three classes of antibiotics [12]. The details of clinical presentation, antibiotic therapy and other relevant information such as CRP (latex CRP Mono Reagent, Life labs, India) and PCT (Chemiluminescence Beckman Coulter, USA) values were recorded. The severity of sepsis was correlated with the levels of the proinflammatory markers, CRP (>100 mg/L) and PCT (>10 ng/mL). The levels of PCT were graded as mild or local bacterial infection (<0.5 ng/mL), SIRS (0.5-1.9 ng/mL), Sepsis (2-10 ng/mL) and severe sepsis (>10 ng/mL) [13].

STATISTICAL ANALYSIS

Percentages were calculated using Microsoft office excel 2013.

RESULTS

Out of the total 4033 urine cultures obtained from suspected UTI patients during the study period, 1402 (34.76%) had significant bacteriuria. Out of 1402 patients, 53 (3.78%) patients also had positive blood cultures with the same organism(s) and hence fulfilled the definition of urosepsis. These 53 patients were included in the study for further analysis. The mean age of the patients was 63.92 years. [Table/Fig-1] shows age and sex distribution of the patients. Of these 53 patients, 37 (69.8%) patients were >60 years of age. The male to female distribution was 1:1.12. (25 Males and 28 Females). Common risk factors for developing urosepsis is shown in [Table/Fig-2]. Out of the 53 patients, 43.4% (23/53) had more than one of the risk factors associated with severe sepsis and poor prognosis.

Age group (years)	Female	Percentage	Male	Percentage	Grand total	Percentage
30-39	1	1.89	0	0	1	1.89
40-49	1	1.89	6	11.32	7	13.21
50-59	2	3.77	6	11.32	8	15.09
60-69	14	26.42	7	13.21	21	39.62
70-79	8	15.09	4	7.55	12	22.64
>80	2	3.77	2	3.77	4	7.55
Grand total	28	52.83	25	47.17	53	100

[Table/Fig-1]: Age and sex distribution table (N= 53).

Risk factor	No of Patients (N=53)	Percentage
Age >60 years	37	69.8
Diabetes	34	64.2
Urinary Catheter	19	35.84
Chronic Kidney Disease	12	26.5
Immunosuppression	4	7.55
Prostatomegaly	6	11.32
Others*	4	7.55

[Table/Fig-2]: Risk factors associated with urosepsis.

*Others- Recurrent UTI, Renal calculi, Cystoscopy.

All 53 patients had a monomicrobial infection (51 GNB and 2 *Enterococcus*). [Table/Fig-3] shows the distribution of the isolates and [Table/Fig-4] shows the antibiotic susceptibility profile of the GNB. There was a 52.94% (27/51) multidrug resistance (Carbapenem resistance) among GNB isolates. Of the 51 GNB isolates, Enterobacteriaceae isolates were 49 (96.08%) and among these, *E. coli* was the commonest isolate (43/49, 87.75%). Of the total 43 *E. coli* isolates, 4/43 (9.3%) were only ESBL producers and 23/43 (53.49%) were ESBL and Carbapenemase producers. Of the total 6 *K. pneumoniae* isolates, 1/6 (16.67%) was only ESBL producer and 3/6 (50%) were ESBL and Carbapenemase producers.

Name of the Organism	Number	Percentage
<i>E. coli</i>	43	81.14
<i>Klebsiella pneumoniae</i>	6	11.32
<i>Pseudomonas aeruginosa</i>	2	3.77
<i>Enterococcus spp</i>	2	3.77
Total	53	100

[Table/Fig-3]: Distribution of isolates.

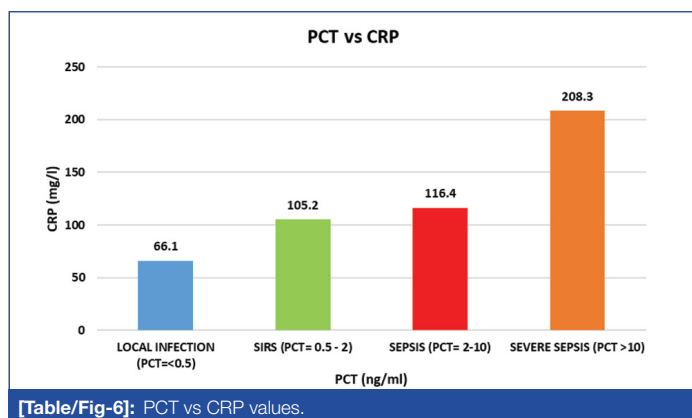
Antibiotic	<i>E. coli</i> (N= 43)		<i>Klebsiella spp</i> (N= 6)		<i>Pseudomonas aeruginosa</i> (N=2)	
	No.	% Susceptible	No.	% Susceptible	No.	% Susceptible
Amoxicillin-clavulanic acid	32	74.4	4	66.6	NA	NA
Piperacillin-tazobactam	32	74.4	4	66.6	0	0
Cefotaxime	16	37.20	2	33.3	NA	NA
Ceftazidime	16	37.20	2	33.3	0	0
Cefepime	16	37.20	2	33.3	0	0
Cefaperazone-sulbactam	32	74.4	4	66.6	0	0
Ertapenem	20	46.51	3	50	NA	NA
Imipenem	20	46.51	3	50	1	50
Meropenem	20	46.51	3	50	1	50
Amikacin	12	27.9	2	33.3	0	0
Gentamicin	12	27.9	2	33.3	0	0
Ciprofloxacin	6	4.65	0	0	0	0
Levofloxacin	6	4.65	0	0	0	0
Colistin	43	100	6	100	2	100

[Table/Fig-4]: Antimicrobial susceptibility pattern of GNB isolates (N=51).

Out of the 53 patients, 75.5% (40/53) progressed to severe sepsis leading to septic shock and multi-organ failure and of which 26/40 (65%) had a fatal outcome {20/26 (77%) females and 6/26 (23%) males}. Severe sepsis and high mortality of 84.6% (22/26), were associated with resistant phenotypes (ESBL and Carbapenemase producers {*E. coli* (23) and *Klebsiella pneumoniae* (3)}. Of the 2 *Pseudomonas aeruginosa* isolates, 1 isolate showed resistance to carbapenems. Both these patients with *Pseudomonas aeruginosa* infection had severe sepsis and a fatal outcome with significant levels of proinflammatory markers (PCT and CRP). In all, there were 2 *Enterococcus* isolates and both were resistant to Beta lactams and Macrolides but susceptible to vancomycin, teicoplanin and linezolid. Both these patients succumbed to the sepsis with significant levels of proinflammatory markers (PCT and CRP). In the present study, as shown in [Table/Fig-5], 22.6% (12/53) had PCT values 2-10 ng/mL (Sepsis) and 28/53 patients (52.8%) had a value of >10 ng/mL (Severe sepsis). A direct correlation between the PCT levels and poor clinical out-come of the patients in these two groups with severe sepsis was noted with a 65% mortality (26/40). A mean PCT of 17 ng/mL and a mean CRP of 194 mg/L were observed in all the 26 patients who succumbed to the urosepsis. Remainder of the PCT values were <0.5 ng/mL among 8 (15.1%) patients (Local infection) and 0.5-2 ng/mL among 5 (9.5%) patients (SIRS) [Table/Fig-5]. [Table/Fig-6] shows a correlation between the PCT and CRP values with the severity

PCT Range	No of Patients (N=53)	No. of Mortality (%)
<0.5 ng/mL	8	NIL
0.5-1.9 ng/mL	5	NIL
2-10 ng/mL	12	3 (5.7%)
>10 ng/mL (Avg value=17.0)	28	23 (43.4%)

[Table/Fig-5]: Showing patient outcome and PCT range.



of sepsis. In case of severe sepsis with a PCT of >10 ng/mL, a proportionate increase of serum CRP was noted with an average of 208.3 mg/l. Similarly, in case of sepsis with PCT of 2-10 ng/mL, the mean CRP was 116.4 mg/l. In case of local infection and SIRS, there was no significant rise of CRP, which was 66.1 mg/l and 105.2 mg/l respectively.

DISCUSSION

Urosepsis resulting from complicated UTI in patients with associated underlying risk factors increases morbidity and mortality. The condition can be usually identified early in its course with a basic diagnostic evaluation comprising of risk factor analysis, urine and blood cultures and proinflammatory marker levels for sepsis. Successful management of patients with urosepsis depends on isolating the causative agent and instituting early and specific antibiotic therapy, along with eliminating the infectious foci in the urinary tract [14].

Age of the patients is one of the risk factors. In the present study, 37/53 (69.8%) of the patients were ≥ 60 years of age with a mean age of 63.92 years, and a mortality of 26/37 (70.3%). Other studies observed a mean age range of 60–83.6 years [15-17], with a mortality rate of 33% [16]. Underlying co-morbid conditions, especially diabetes mellitus has been shown to be associated with development of pyelonephritis and further progressing to urosepsis [15,18]. In the present study, Type 2 DM was a major risk factor among 34/53 (64%) patients. Of the 34 diabetic patients, 32/34 (94.11%) were elderly patients (>60 years), of which 23 patients (71.88%) died of urosepsis.

In the present study, all the 53 cases were of monomicrobial infections with GNB being the predominant isolates 51/53 (96.2%). *E. coli* was the commonest causative organism, 43/53 (81.1%). The isolation rate of *E. coli* from other studies were 46.1% [16], 69% [19], 75% [15] and 79% [17]. Multidrug resistant urosepsis is being increasingly reported in various studies [15,19]. This can be attributed to recurrent infections, repeated hospitalisations of the patients and indiscriminate use of antibiotics [20].

PCT is a valuable proinflammatory marker in the diagnosis of bacterial sepsis, determining the severity of sepsis and the duration of antibiotic administration [21]. During an infection, PCT is released up to a thousand fold increase from nearly all tissues and cell types in the host in response to cytokines and bacterial products [22]. Patients with urosepsis and shock also exhibit a significantly higher CRP as compared with urosepsis patients without shock [22-24]. A direct correlation between the levels of PCT and CRP in sepsis and septic shock and mortality was also documented by Brunkhorst FM et al., [22].

In the present study, 40/53 (75.5%) patients progressed to severe sepsis leading to septic shock and multi-organ failure. A mean PCT of 17 ng/mL and a mean CRP of 194 mg/l were observed in all the 26/53 patients who succumbed to the urosepsis, in the present study. The values were low among the survivors, as was also documented by another Indian study (PCT of 12 ng/mL

[23]. and the mortality rate of the patients associated with these resistant isolates was 22/26 (84.6%) [23,24].

There is high mortality rate associated with Multidrug resistant organisms (MDROs) for which a combination therapy of carbapenem plus a Polymyxin B would be effective. Similar studies done on MDROs causing blood stream infections showed a 2-3 fold increase in mortality rate and treatment failure [25,26]. To decrease the mortality rate among MDROs various studies [27,28], have shown effective therapy in such cases to be a combination therapy with Carbapenem plus a Polymyxin B compared to monotherapy.

Limitation(s)

This study had certain limitations. There was no control group, (UTI with negative blood cultures) to compare the risk factors and values of the biomarkers which can further improve the diagnosis for the clinicians in order to treat patients on risk.

CONCLUSION(S)

Early recognition of symptoms followed by accurate diagnosis and early goal directed therapy is essential to decrease morbidity and mortality from urosepsis. Patients with existing co-morbid conditions must be educated on the possible risk of UTI leading to urosepsis. They must be advised to seek early intervention in order to avoid poor outcome. A multidisciplinary team including microbiologists, surgeons, infectious disease physicians and radiologists with a coordinated effort is essential for a favourable outcome.

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PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Department of Microbiology, Kamineni Academy of Medical Sciences, Hyderabad, Telangana, India.
2. Assistant Professor, Department of Microbiology, Kamineni Academy of Medical Sciences, Hyderabad, Telangana, India.
3. Professor, Department of Microbiology, Kamineni Academy of Medical Sciences, Hyderabad, Telangana, India.
4. Professor, Department of Microbiology, Kamineni Academy of Medical Sciences, Hyderabad, Telangana, India.
5. Professor, Department of Microbiology, Kamineni Academy of Medical Sciences, Hyderabad, Telangana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Lakshmi Vemu,
Professor, Department of Microbiology, Kamineni Academy of Medical Sciences,
LB Nagar, Hyderabad, Telangana, India.
E-mail: lakshmi57vemu@gmail.com

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