

## Brief Original Article

# Empiric antibiotic and in-vitro susceptibility of urosepsis pathogens: do they match? The outcome of a study from south India

Anandhalakshmi Subramanian<sup>1</sup>, Sandhya Bhat<sup>2</sup>, Sudhagar Mookkappan<sup>3</sup>, Patricia Anitha<sup>2</sup>, Ravichandran Kandasamy<sup>4</sup>, Reba Kanungo<sup>2</sup>

<sup>1</sup> Department of Microbiology, College of Medicine King Khalid University Abha, Saudi Arabia

<sup>2</sup> Department of Microbiology, Pondicherry Institute of Medical Sciences, Puducherry, India

<sup>3</sup> Department of General Medicine, Pondicherry Institute of Medical Sciences, Puducherry, India

<sup>4</sup> Department of Biostatistics, Pondicherry Institute of Medical Sciences, Puducherry, India

### Abstract

**Introduction:** Urosepsis is life threatening, unless treated immediately. Empirical treatment with appropriate antibiotics lowers the risk of a poor outcome. However, with increasing resistance among common uropathogens, there is a need for continuous review of the existing protocol to determine whether there is a correlation between empirical antibiotic therapy and in-vitro susceptibility pattern of the pathogens causing urosepsis.

**Methodology:** A prospective study was carried out on 66 confirmed cases of urosepsis from January 2017 to December 2018 after obtaining ethical clearance. Demographic details, risk factors, length of hospital stay, bacteriological profile, empirical antibiotic given, and change in antibiotic following susceptibility report and outcome was recorded.

**Results:** Among the 66 urosepsis cases 63 of them were started on empiric antibiotic. The correlation between the empirical antibiotic given and the in-vitro antimicrobial susceptibility was found to be significant with a  $p$  value  $< 0.0001$ . Among the 63 for whom empiric antibiotics was started further escalation of antibiotic was done in 46 patients. The remaining 20% of cases were changed over to a different antibiotic, in line with susceptibility report. The mortality rate was (15.1%) with a confidence interval of (CI =  $15 \pm 3.5$ ). The association between the risk factors for urosepsis and their effect on mortality rate was analyzed. Diabetes mellitus and chronic kidney disease were identified as important independent risk factors and had direct influence on the mortality rate with significant  $p$  value of 0.0281 and 0.0015 respectively.

**Conclusions:** A significant correlation was identified between the empirical antibiotic given and in-vitro antibiotic susceptibility pattern.

**Key words:** Urosepsis; empirical antibiotic; invitro antimicrobial susceptibility; risk factors.

*J Infect Dev Ctries* 2021; 15(9):1346-1350. doi:10.3855/jidc.14589

(Received 29 December 2020 – Accepted 07 March 2021)

Copyright © 2021 Subramanian *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### Introduction

Urosepsis is a complication of infection originating from the urinary tract; often fatal unless treated immediately, Urosepsis accounts for almost 25% of total sepsis cases among adults [1]. It has been found that the site of infection is the urinary tract in approximately 10–44% of cases of severe sepsis or septic shock [2,3]. Further urosepsis is associated with a high mortality rate of about 20–40%, hence early diagnosis and prompt treatment is vital. Empirical treatment with appropriate antibiotics lowers the risk of a poor outcome [4]. Decision to start the empiric antibiotic based on the suspicion of the organism causing the infection remains a major challenge to clinicians treating the patient with urosepsis [5]. Conventionally, this has been accomplished by the available antibiogram of common pathogens causing infections at the local hospital level, and the assessment

of specific patient types, which in turn is likely to guide the clinicians to start the empirical broad-spectrum antibiotics [6]. However, with increasing resistance among common uropathogens, there is need for continuous review of the existing protocol. This study was undertaken with the objectives to determine the bacteriological profile, antibiotic susceptibility pattern of uropathogens and to correlate the susceptibility patterns of these uropathogens with the empiric therapy used for patients and to determine the outcome associated with urosepsis.

### Methodology

A prospective study was carried out from January 2017 to December 2018 at a tertiary care hospital at Puducherry in South India after obtaining institute ethical clearance on 11/11/2016 by PIMS Institute Ethics committee Ganapathichettikulam Kalapet

Puducherry. Reg. with ECR/400/Ins/PY/2013RR16 (EC:RC16/136). Urosepsis was confirmed based on simultaneous positive urine and blood culture from the patient with the same pathogen and susceptibility. Both the urine and blood samples of the patients were collected prior to administration of antibiotic. A semi quantitative method of analysis was done for urine culture. Blood culture was done using a BacT/ALERT 3D machine (Biomerieux Inc. Durham, USA) which is an automated continuous monitoring system. Further identification of the pathogen was done using standard biochemical tests. Antibiotic susceptibility pattern was performed as per Clinical Laboratory Standard guidelines 2017. Among a total of 3,432 patients, who had culture proven urinary tract infection, 66 were confirmed cases of urosepsis. Demographic details, risk factors, length of hospital stay, bacteriological profile, empirical antibiotic given, and change in antibiotic following susceptibility report and outcome was recorded.

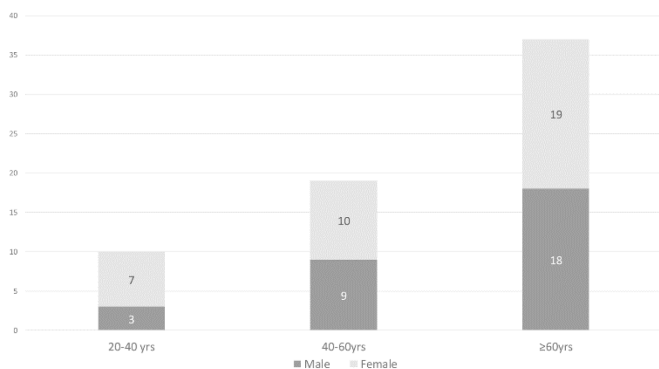
**Statistical analysis**

Categorical variables were reported using n (%); while continuous variables using mean ± SD or median. Univariate analysis was performed using the chi-square test for categorical variables. In the univariate analysis, all variables were considered as independent variables and a binary logistic regression model was applied.

**Results**

Among the 3,432 culture proven cases of urinary tract, urosepsis accounted for 1.9% (95% confidence interval, CI 0.8 to 4.6). And out of the 1.9% (66), 62 were community acquired and 4 were hospital acquired urosepsis cases. A total of 56% (n = 37) belonged to the age group of ≥ 60 years. of age (Figure 1). The median age of the patients with urosepsis was found to be 63 years with an interquartile range (IQR) of 53 to 74

**Figure 1.** Age and Sex wise distribution of urosepsis cases (n = 66).

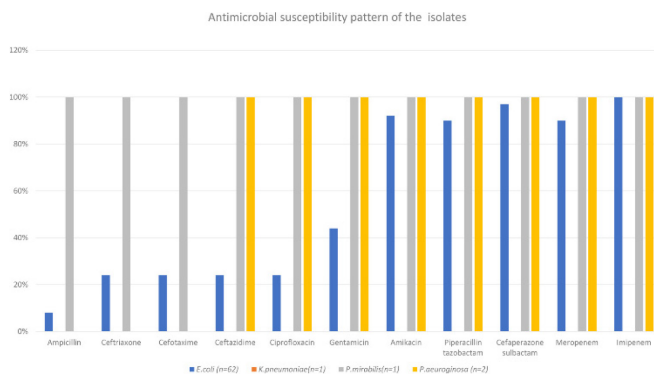


years. Male to female ratio was found to be equal. But it was noted that among the nine females who were in the reproductive age group (20-45 years), five of them had developed urosepsis following childbirth during the puerperal period.

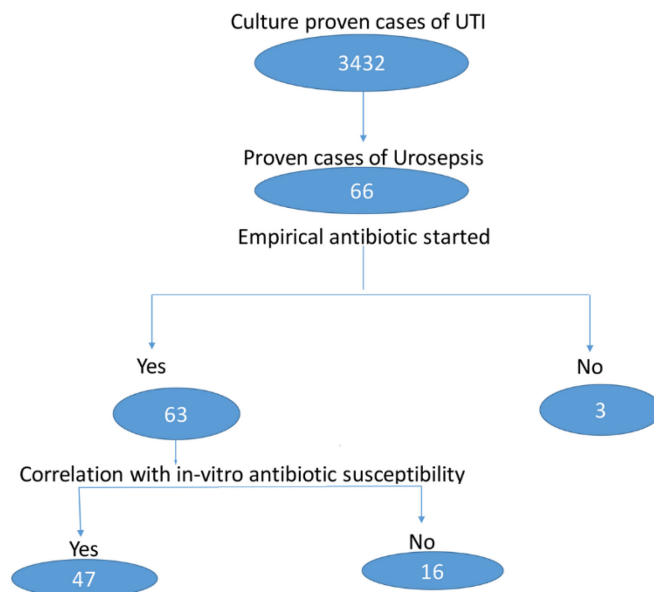
Fever was the predominant presenting symptom. About 95% patients presented with fever along with other associated findings such as dysuria, hematuria, chills and rigors, lower abdominal pain, loin pain, decreased urine output, urinary retention, anasarca and seizures.

*Escherichia coli* was the predominant isolate (94%) followed by *Klebsiella pneumoniae* (3%), *Proteus mirabilis* (1.5%) and *Pseudomonas aeruginosa* (1.5%). Organisms showed least resistance to imipenem (1.5%) followed by cefoperazone – sulbactam (11%) and piperacillin - tazobactam (8%) (Figure 2). Among urosepsis cases 63 of them were started on empiric

**Figure 2.** Antimicrobial susceptibility pattern of the isolates.



**Figure 3.** Flow chart of case enrolment and analysis.



**Table 1.** Correlation between empirical antibiotic given and the in-vitro antimicrobial susceptibility report (n = 63).

Antibiotics given empirically	Correlation with in vitro susceptibility		Total (n = 63)
	Correlated	Not Correlated	
Ampicillin	0	2	2
Cephalosporins(Cefotaxime,cefazolin&ceftriaxone)	1	8	9
Fluoroquinolone	0	4	4
β -lactam/β-lactamase inhibitor	41	2	43
Amikacin	1	0	1
Imipenem	4	0	4
<i>p</i> value	< 0.0001		

antibiotic. Seventy five percent of the empirical antibiotics given were found to be susceptible in vitro. (Figure 3)

Among the empiric antibiotics used there was maximum correlation with the in vitro susceptibility among the patients who were started on β-lactam/β-lactamase inhibitors (Table 1). Further the correlation between the empirical antibiotic given and the in vitro antimicrobial susceptibility report was analyzed by univariate analysis using chi-square test and was found to be significant with a *p* value < 0.0001. Among the 63 for whom empiric antibiotics was started further escalation of antibiotic was done in 46 patients, either due to clinical deterioration or based on the in-vitro susceptibility pattern.

Remaining 26.9% of cases were changed over to a different antibiotic, in line with the susceptibility report. Distribution of underlying comorbid conditions among 66 patients of urosepsis in the descending order was diabetes mellitus (44/66; 66.6%), chronic kidney disease (19/66; 28.7%), catheter in-situ (10/66; 15.1%), benign prostatic hypertrophy (6/66; 9%), ureteric calculi (3/66; 4.5%), vesicoureteral reflex (2/66; 3%) and phimosis (1/66; 1.5%). We analyzed the risk factors as independent variables and their association with mortality rate by calculating relative risk (RR), its

standard error and 95% confidence interval according to Altman (Table 2).

On analysis of the risk factors diabetes mellitus and chronic kidney disease were not only identified as important independent risk factors but also had a direct influence on the mortality rate with significant *p* value of 0.0281 and 0.0015 respectively. While the risk factors like age > 60 years, sex and inappropriate antibiotic therapy did not have any significant association on the mortality rate.

Twenty-three (35%) of these patients had acute kidney injury (AKI) either at admission or during the course of treatment with three requiring emergency hemodialysis. The median duration of hospital stay was found to be eight days (IQR 5 to 15 days). The mortality rate was 15.1%, with a confidence interval of CI = 15 ± 3.5. The correlation between the empiric antibiotic given and in-vitro susceptibility test among these patients who expired was found to be 70% (Table 3).

## Discussion

Our study proved a significant correlation between the empirical antibiotic used and the in-vitro susceptibility pattern for the pathogen causing urosepsis. Urosepsis accounts for 20- 30% of all sepsis cases [6,7]. It is crucial to recognize urosepsis rapidly and to provide timely, effective treatment, as delayed

**Table 2.** Association between the risk factors for urosepsis and their effect on mortality rate.

Risk factors	nDeath/N exposed	95% CI	<i>p</i> value
<b>Age</b>			
> 60 years	6/37	0.5394 to 1.6183	<i>p</i> = 0.8085
< 60 years	4/29		
<b>Sex</b>			
Male	6/30	0.4280 to 1.3408	<i>p</i> = 0.3405
Female	4/36		
<b>Diabetes mellitus</b>			
Yes	9/44	0.5666 to 0.9683	<i>p</i> = 0.0281
No	1/22		
<b>Chronic kidney disease</b>			
Yes	7/19	0.2323 to 0.7066	<i>p</i> = 0.0015
No	3/48		
<b>Inappropriate antibiotic</b>			
Yes	3/16	0.3001 to 2.3881	<i>p</i> = 0.7529
No	7/47		

treatment results in 7.6% increase in mortality [7,8]. The mortality rate of urosepsis by various studies ranges from 20- 40% [6]. The prevalence of urosepsis among cases with urinary tract infection (UTI) was found to be 1.9% CI (95% confidence interval (CI) 0.8 to 4.6). This in comparison with a previous study done in the same locality which had a prevalence rate of 3.8%, indicates that it is slightly decreasing [9]. Even with the low prevalence of urosepsis among cases of UTI, the mortality due to the same can be as high as 40% [4]. But in our study, it was 15.1% which is comparatively less. The low mortality rate could be attributed to 75% correlation between the empirical antibiotic used and the in-vitro susceptibility pattern for the pathogen isolated. A similar correlation was found in another study in which empiric antibiotics were inappropriate in 31.6% of cases [3]. Further it has been identified as a marker independently influencing the mortality rate in sepsis [3]. As well the correlation between the empiric antibiotic given and in-vitro susceptibility test among these patients who expired was found to be 70%. Which indicates that even though the optimum drug was given there had been other comorbid conditions which increased the mortality rate. The major complications which were associated with the mortality of the patients due to urosepsis were found to be bilateral emphysematous pyelonephritis (2), bilateral Hydroureteronephrosis (1), peritonitis (1) and pleural effusion (1). While other comorbid conditions like post renal transplant, SLE, malignancy, lithium toxicity and cerebrovascular accident was the baseline cause of death in remaining patients. Further all these patients had either diabetes mellitus or chronic kidney disease as an associated comorbid condition which as mentioned earlier had a direct effect on mortality. Regardless of increasing incidence, the mortality due to urosepsis has evidently dropped, which could be attributed to the institution of strategies. Further the usage of appropriate empirical antibiotic and adherence to susceptibility report could have been the other whys and wherefores for lesser mortality rate. Usage of cefoperazone-sulbactam and piperacillin-tazobactam as empirical antibiotic followed by changeover based on susceptibility report had an overall favorable outcome.

Similar to other studies *E.coli* was found to be the most common organism associated with urosepsis [9,10]. It has been reported to be the commonest organism in overall sepsis cases, reason being the focus is in urinary tract in almost 40% of the cases [3,11] In our study we had an equal distribution of cases in both sexes, whereas male preponderance is reported in another study [9]. One of the important findings was that among the 9 females who were in reproductive age group (20-45 years) 5 of them had developed urosepsis following childbirth during the puerperal period. That is 25% (9) females were in the reproductive age group and among them 55% (5) of them were in the puerperal period, indicating urosepsis to be one of the commonest causes of puerperal sepsis.

Urosepsis is common in elderly population, and it is reported that more than 60% of the patients who develop severe sepsis are older adults above 65 years of age [12-14].

Similarly, we found median age of the patients with urosepsis to be 63 years with an interquartile range (IQR) 53 to 74 years. It has been estimated that older adults are 13 times more at a risk of developing sepsis and mortality rate in them is doubled [15]. Thus, urosepsis in elderly has been a well-established risk factor [11,13]. And the factors associated with it include other co-morbid conditions like diabetes and chronic kidney disease. In correlation with other studies the most common comorbid conditions associated with development of urosepsis was found to be diabetes mellitus (66%). It has been studied that the patients with diabetes mellitus often developed bacteraemia and that the common focus of infection was urinary tract [16]. The two recognised cause for development of sepsis in diabetic patients include increased glycosuria driving the growth of organisms and the dysfunctional neutrophil with sluggish chemotaxis, adhesion and intracellular killing [15]. Further in the study we also found that the risk factors like diabetes mellitus and chronic kidney disease, as independent variables had a direct association with the increased mortality rate.

## Conclusions

In conclusion we observed that there is decrease in the prevalence of urosepsis, while elderly age, diabetes

**Table 3.** Correlation between empiric antibiotic and susceptibility pattern of organisms in patients with urosepsis who expired.

Empirical antibiotics given	Correlated	Not correlated	Total (n = 10)
Piperacillin /tazobactam	3	2	5
Cefoperazone /sulbactam	3	0	3
Ampicillin	0	1	1
Imipenem	1	0	1
Total (n = 10)	7	3	10

mellitus and chronic kidney disease being the major associated comorbid conditions. And among them diabetes and chronic kidney disease had significant association with the mortality rate. A significant correlation was identified between the empirical antibiotic given and in-vitro antibiotic susceptibility pattern. Further this was the basis for low mortality rate as compared to other studies. Further initiation of empiric therapy in patients presenting with septic shock instantly after collection of diagnostic specimens is also recommended. Use broad-spectrum antimicrobial agents as initial empiric therapy sometimes with a combination of antimicrobial agents based on the local antibiogram is essential. Hence continuous review of current antimicrobial susceptibility of pathogens and implementation of empirical antibiotic based on it in serious infections, such as urosepsis, must be the cornerstone in management.

The study highlights the findings of an important life-threatening condition namely urosepsis. Considering the poor outcome of patients not appropriately treated for this condition it is essential to continuously monitor the empiric treatment and subsequent change in antibiotic based on the antibiogram of the isolate which is again reiterated in this study. Hence it is recommended that isolates causing urosepsis be analysed from time to time to effectively frame policies for empiric treatment of these infections.

## References

1. Bonkat G, Pickard R, Bartoletti R, Bruyère F, Geerlings S, Wagenlehner F, Wullt B (2017) EAU guidelines on urological infections. European Association of Urology (ISBN 978-90-79754-91-5).
2. Wagenlehner FME, Weidner W, Naber KG (2007) Optimal management of urosepsis from the urological perspective. *Int J Antimicrob Agents* 30: 390–397.
3. Ramos-Rincón JM, Fernández-Gil A, Merino E, Boix V, Gimeno A, Rodríguez-Díaz JC, Valero B, Sánchez-Martínez R, Portilla J (2019) The quick Sepsis-related Organ Failure Assessment (qSOFA) is a good predictor of in-hospital mortality in very elderly patients with bloodstream infections: a retrospective observational study. *Sci Rep* 9: 15075.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerf B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 43: 304–377.
5. Alhashem F, Tiren-Verbeet NL, Alp E, Doganay M (2017) Treatment of sepsis: what is the antibiotic choice in bacteremia due to carbapenem resistant Enterobacteriaceae? *World J Clin Cases* 5: 324–332.
6. Dreger NM, Degener S, Ahmad-Nejad P, Wöbker G, Roth S (2015) Urosepsis - Etiology, diagnosis, and treatment. *Dtsch Arztebl Int* 112: 837–848.
7. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 34: 1589–1596.
8. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, Lemeshow S, Osborn T, Terry KM, Levy MM (2017) Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med* 376: 2235–2244.
9. Bijou MR, Bhat KS, Kanun R (2016) Characteristics of blood stream isolates in urosepsis from a tertiary care hospital. *Int J Curr Microbiol App Sci* 5: 424–431.
10. Hsiao C-Y, Yang H-Y, Chang C-H, Lin H-L, Wu C-Y, Hsiao M-C, Hung P-H, Liu S-H, Weng C-H, Lee C-C, Yen T-H, Chen Y-C, Wu T-C (2015) Risk factors for development of septic shock in patients with urinary tract infection. *Biomed Res Int* 2015: 717094.
11. Peach BC, Garvan GJ, Garvan CS, Cimiotti JP (2016) Risk factors for urosepsis in older adults: a systematic review. *Gerontol Geriatr Med* 2: 2333721416638980.
12. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29: 1303–1310.
13. van Nieuwkoop C, Bonten TN, van't Wout JW, Kuijper EJ, Groeneveld GH, Becker MJ, Koster T, Wattel-Louis GH, Delfos NM, Ablj HC, Leyten EM, van Dissel JT (2010) Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study. *Crit Care* 14: R206.
14. Kaukonen K-M, Bailey M, Suzuki S, Pilcher D, Bellomo R (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. *JAMA* 311: 1308–1316.
15. Balasoiu D, van Kessel KC, van Kats-Renaud HJ, Collet TJ, Hoepelman AI (1997) Granulocyte function in women with diabetes and asymptomatic bacteriuria. *Diabetes Care* 20: 392–395.
16. Schneeberger C, Holleman F, Geerlings SE (2016) Febrile urinary tract infections: pyelonephritis and urosepsis. *Curr Opin Infect Dis* 29: 80–85.

## Corresponding author

Dr. Anandhalakshmi Subramanian MBBS, MD Microbiology, Assistant Professor, Department of Microbiology, College of Medicine, King Khalid University, 61421 Abha, Saudi Arabia  
Phone: +966530810096  
Email: anandhalakshu@gmail.com

**Conflict of interests:** No conflict of interests is declared.