# Clinical Spectrums of *Salmonella Bacteriuria* in Renal Transplant Recipients

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## Introduction

Pakistan is an endemic area for *salmonella* infection.[1] Enteric fever and salmonellosis are the most common clinical presentations. Asymptomatic carriers are found to be associated with shedding of antigens usually through the gastrointestinal tract and rarely through the urinary tract.[2] Chronic carrier state of *Salmonella* has been associated with immunosuppression, stone disease, structural abnormalities and associated infection e.g. Schistosomiasis.[3]

Our center is the largest renal transplant facility in Pakistan where over 3400 live related renal transplant have been performed. Infection in renal transplant recipients contributes significantly to their mortality and morbidity.[4] *Salmonella bacteriuria* is a rare finding even in endemic regions and reports in renal transplant recipients are scarce.[5] We have observed variable clinical findings in patient having *Salmonella* species in their urine cultures. The purpose of this study is to observe the incidence of *Salmonella bacteriuria* and its clinical spectrum in our renal transplant recipients.

## Material and Method

This was an observational retrospective study conducted over a period of two years from July 2009 to July 2011in renal transplant recipients with positive urine culture. Culture reports were retrieved from the laboratory data base. Each positive urine culture report with *salmonella* species was considered as a separate episode. Urine cultures, if repeatedly positive within 15 days in the same patient were excluded.

Urine culture and urinalysis are part of routine laboratory testing for all transplant patients at their follow up clinic visit at our center.

Patients' files were reviewed for history of fever, dysuria, graft tenderness, antibiotic treatment and its duration at the time of each episode. Laboratory parameters including pyuria, total leukocyte count, serum creatinine level and blood culture positivity were noted.

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All mid-stream urines (MSU) were processed for quantitative analysis using calibrated 0.001ml (1µl) disposable plastic loops and inoculated by Quadrant Technique on CLED (Cystine Lactose Electrolyte-Deficient) Agar. Plates were incubated overnight at 37°C at ambient air. With 0.001 ml loop, one colony equals 1,000CFU/ml and 100 colonies would be equal to 100,000 CFU/ml. Bacterial count of $\geq 10^5$ CFU/ml of single morphotype were considered significant. Routine biochemical tests and serotyping using conventional antiserawere used for *Salmonella* species identification. Antibiotic susceptibility testing was performed with Kirby-Bauer disc diffusion method using Clinical laboratory standard institute (CLSI) standards.

### Definitions

*Salmonella bacteriuria*
Urine culture positive for *Salmonella* species with or without clinical sign and symptoms and abnormal laboratory parameters.

### New episode

Positive urine culture at least 4-6 weeks after enteric fever or salmonellosis or last positive urine culture positive for *Salmonella* species.

### Asymptomatic bacteriuria

Isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen from an individual without symptoms or signs of urinary tract infection.

### Inclusion criteria

All urine samples collected as mid-stream specimen and positive for *Salmonella* species from all age groups.

### Exclusion criteria

All urine cultures which came positive within recent (4-6 weeks) documented episodes of enteric fever (positive blood cultures)

## Result

Eighteen renal transplant recipients were found to have *Salmonella bacteriuria,* representing 0.06% of total positive urine culture in this time period.

Out of 18 patients, urine cultures of 16 patients were positive for typhoid causing *Salmonella* species (S.*typhi* and S.*paratyphi*) while non-typhoidal *Salmonella* species were detected in the

urine of 2 patients.

Two patients had blood culture proven typhoid infection while other 2 had Salmonellosis with stool culture positive with in last 2 months duration.

Total 34 episodes were recorded from 18 patients during the study duration (Table 1).

Clinical presentations and laboratory parameters were variable in all episodes of patients (Table 2).

Clinical features of pyelonephritis, fever with chill, dysuria and graft site tenderness with positive blood cultures were present in only 3 patients. Graft biopsy was not performed in these patients However; histopathological proven florid pyelonephritis supported by the relevant clinical findings and laboratory parameters was found in two patients (11%).

**Table 1. Description of symptomatic and asymptomatic episodes (N=34)**

| No. of Patients | No. of symptomatic episodes (N) | No. of asymptomatic episodes (N) |
|---|---|---|
| **9** | 1 | 0 |
| 3 | 1 | 2 |
| 3 | 2 | 0 |
| 1 | 4 | 0 |
| 1 | 0 | 4 |
| 1 | 1 | 1 |
| 18 | 23 (68%) | 11(32%) |

**Table 2. Summary of clinical features and laboratory parameters**

| **Clinical Features** | N (%) |
|---|---|
| Fever with dysuria | 09 (39) |
| Only fever | 06 (26) |
| Fever, graft tenderness, dysuria | 06 (26) |
| Only dysuria | 02 (09) |
| **Laboratory Parameters** | **N (%)** |
| Pyuria, rise in creatinine | 05 (22) |
| Pyuria, rise in creatinine, rise in TLC, positive blood culture | 04 (17) |
| Pyuria, rise in creatinine, rise in TLC | 03 (13) |
| Only rise in creatinine | 04(13) |
| Only pyuria | 02 (09) |
| Only rise in TLC | 01 (04) |
| Pyuria,, rise in TLC | 01 (04) |
| No laboratory finding | 03 (13) |

Patients with all symptomatic episodes were treated for an average duration of 14 days. Five patients have recurrent episodes despite adequate treatment. Only a single episode of asymptomatic bacteriuria was treated because no other cause of elevated creatinine was identified.

Among 16 typhoid causing *Salmonella* species, 11(69%) were resistant to ciprofloxacin, whereas MDR (resistant to ampicillin, Co-trimoxazole and chloramphenicol) strain were 4 (25%). No ceftriaxone resistant strain was detected in any episode during the study duration.

**Discussion**

Infections of *Salmonella* species could be intestinal and extra intestinal. High incidence of UTI in renal transplant recipient is due to abnormal structure, high immunosuppression[6] and instrumentation. The incidence of *salmonella bacteriuria* in our renal transplant recipients is 0.06%. Variable incidence rate has been observed among different population with different levels of immune status. Hsu *et. al* reported the incidence of 1.5% in heart transplant recipients.[7] The incidence of *Salmonella bacteriuria* by Nwadioha et.al in Nigerian general population is 2%.[8] Tena D *et.al* had reported 0.056% non-typhoidal *Salmonella* urinary tract infection in immunosuppressed hospitalized population.[9]

In most studies, non-typhoidal *Salmonella* (NTS) strains have been reported causing urinary tract infection.[10, 11] However, typhoid causing *Salmonella* was the dominant pathogen in our study population.

Spectrum of clinical features in renal transplant recipients could be variable. In this study, we found that it ranges from simple asymptomatic bacteriuria to florid pyelonephritis. Fever and dysuria was the most common presenting feature, however, fever could be the only presenting symptom without localized systemic sign symptoms and abnormal laboratory parameters. Graft tenderness with fever and dysuria suggesting graft pyelonephritis was the next most common presenting feature. These clinical findings of graft pyelonephritis were supported by laboratory parameters such as pyuria, rise in creatinine, rise in TLC, positive blood culture.

Recurrent symptomatic episodes might be possibility due to abnormal urinary tract along with severe immunosuppression.[12] Biofilm formation could be the possible reason of chronic carrier and delayed clearing according to Raza A *et.al.*[13] Renal stones in native kidney, obstructive uropathy and post-transplant stenting may be the nidus for biofilm formation and hence causing chronic carrier and delayed clearance. We observed symptomatic and asymptomatic episodes in our patients as well.

Pakistan is categorized as a highly-prevalent area of *Salmonella enterica* serovar, having significant carrier rate.[2] High immunosuppression and surgical intervention can activate and lead to overt infection. In this study group, only four patients has history of blood and stool culture proven *salmonella* infection with in last 4-6 weeks, but the rest did not have any recent history of fever of unknown origin or abdominal discomfort suggestive of enteric and Salmonellosis.

Presence of multi-drug resistance bacteria including high resistance rate against Ciprofloxacin in our study also reflect overall resistance pattern in Pakistan.[14] All isolates were susceptible to ceftriaxone. Most of patients were treated for average 14 days, however, symptomatic episodes were observed in 5 patients despite adequate treatment. Therefore, in case of relapse, clinician can consider to extend the total treatment duration.

Impact of level of immunosuppression and recurrence was not evaluated and therefore a major limitation of study and need to evaluate in further studies.

There are some limitations of our study. It was a retrospective study and patient's clinical details were gathered from their files, in which some time have patchy and inconsistent details. It was only two years data, in which sample size was scarce and therefore the pattern of frequency and details of episodes is not dependable for a clinician to take any decision.

**Conclusion**

Effect of *Salmonella* species, especially typhoid strains, is variable from asymptomatic episode to simple cystitis and graft pyelonephritis. If not treated properly, it may lead to serious consequences such as deteriorating graft function and even graft rejection. Due to its high resistance against *salmonella* species, ciprofloxacin should be avoided as empirical therapy.

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