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Nosocomial Urinary Tract Infection in HIV positive and HIV negative Patients in a Tertiary Care Hospital in West Bengal

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ABSTRACT

Nosocomial infections or healthcare-associated infections happen in patients under medical care, which constitute nearly 50% of all hospital infections. Human Immunodeficiency Virus (HIV) infected patients are more prone to get infected in hospitals. In the present study, the frequency of different bacteria causing Nosocomial Urinary Tract Infection (NUTI) among HIV positive and HIV negative groups were investigated. 80 immunocompetent and 80 immunocompromised (HIV/AIDS) admitted patients, who had developed signs and symptoms of UTI after 48 h onwards from the day of admission, were selected for the study. There was significant variation ($p<0.001$) between the presenting symptoms of the two groups, especially, dysuria. Escherichia coli were the predominant microorganism found in the urine of both groups. Other than that, Acinetobacter spp., Morganella morganii, Serratia marcescens, and Staphylococcus epidermidis were only noted in HIV-positive patients. Serratia marcescens has been newly identified in the host institution as a urinary tract pathogen. Perhaps, ampicillin, amoxicillin, clavulanic acid, cephalosporins, nitrofurantoin, co-trimoxazole were significantly resistant among gram-negative isolates. These findings could be attributed to the fact that the immune systems were more vulnerable in HIV-positive groups, making them susceptible to organisms that are not generally considered pathogenicy.

Keywords: Nosocomial infections, Human Immunodeficiency Virus (HIV), Urinary Tract Infections (UTI), Bacteraemia, Drug resistance, Antibiotics

Abbreviations: AIDS: Acquired Immunodeficiency Syndrome, HIV: Human Immunodeficiency Virus, UTI: Urinary Tract Infections, NUTI: Nosocomial Urinary Tract Infections, WHO: World Health Organization, CFU: Colony Forming Unit, CLSI: Clinical and Laboratory Standards Institute, CONS: Coagulase Negative *Staphylococci*

INTRODUCTION

The nosocomial infection is also called hospital-acquired infection or healthcare-associated infection. It is applied to any clinical infection that was neither present nor was in its incubation period when the patient entered the hospital [1]. Despite significant efforts made to prevent nosocomial infections, there is more work required to control these infections. It occurs worldwide and affects both developed and resource-poor countries. In USA and Europe, the incidence density was ranged from 13 to 20 per thousand patients per day [2]. With increasing infections, there is an increase in prolonged hospital stay, long-term disability, increased antimicrobial resistance, increase in socio-economic disturbance, and increased mortality rate [3]. One study showed that the overall increase in the duration of hospitalization for patients with surgical wound infections was 8.2 days, ranging from 3 days for gynecology to 9.9 for general surgery and 19.8 for orthopedic surgery [4]. According to WHO, approximately 15% of all hospitalized patients suffer from these infections [5]. These infections are responsible for 4% to 56% of all death caused in neonates, with an incidence rate of 75% in South-East Asia and Sub-Saharan Africa [5,6]. Nosocomial infections may also be considered either endemic or epidemic. Endemic infections are most common. Epidemic infections occur during outbreaks, defined as an unusual increase above the baseline of a specific infection or infecting organism. The most frequent types of infections include (i) central line-associated bloodstream infections, (ii) catheter-associated urinary

tract infections, (iii) surgical site infections, and (iv) ventilator-associated pneumonia [7,8]. Nosocomial Urinary Tract Infections (NUTI) by *E. coli*, *Klebsiella spp*., *Proteus spp*., *Staphylococci*, *Pseudomonas aeruginosa*, *Enterococci* are constituted nearly 50% of all hospital infections [9]. Highly resistant bacteria or multidrug-resistant Gram-negative bacteria are one of the key causes of high incidence rates of NUTI worldwide [10]. Moreover, HIV-positive patients are more prone to infection in the hospital and therefore a foremost challenge to the patients' safety. The rate of UTI particularly related to the use of urinary catheters plays a significant role in nosocomial infection in HIV patients [11,12]. To determine the frequency of different bacteria causing NUTI in immunocompetent patients is a thrust area of research. Therefore, this study aimed to find out the frequency of different bacteria causing NUTI and compares their antibiotic sensitivity pattern among HIV+ and HIV- patients, being admitted to the hospital for different health-related issues.

MATERIALS AND METHODS

The present observational case-control study was conducted among hospital admitted patients in the School of Tropical Medicine, Kolkata for any particular reason and developed signs and symptoms of UTI after 48 h onwards from the day of admission. The study was conducted (April 2014 to March 2015) after receiving the approval from Institutional Ethics Committee (CREC-STM/64/2013). Adult patients of either sex, both immunocompromised (HIV positive patients) and immunocompetent (HIV negative patients) acquiring UTI 48 h after getting admitted to this hospital and who did not receive antibiotics, at least prior 48 h were selected after receiving their written consent. The exclusion criteria of this study were (i) absence of NUTI, (ii) under any antibiotic or corticosteroid therapy, (iii) having severe dehydration, or (iv) urinary tract abnormalities (anatomical).

Immunocompetent and immunocompromised (HIV/AIDS) admitted patients developing signs and symptoms of UTI after 48 h onwards from the day of admission were recruited for the study and their urine samples were collected for routine urine analysis as also for urine culture and sensitivity examinations. Gram staining was done from a urine sample (without centrifuge) and examined under a microscope for bacteria and pus cells. In urine culture, colony count was performed on blood agar and the numbers of CFUs (Colony Forming Unit) were multiplied by 100 to determine the number of microorganisms per millimeter in the original specimen. On the culture of urine study, a colony count of $\geq 10^5$/ml organisms was considered significant. All the suspected isolates were further sub-cultured on a nutrient agar plate for the identification of microorganisms by (i) Gram's staining, (ii) standard biochemical tests (catalase test, nitrate reduction test, Hugh-Leifson test, sugar fermentation test, methyl red test, citrate utilization test, indole test, urease test, decarboxylase test, phenylalanine deaminase test, oxidase test, triple sugar iron agar test, coagulation test) and (iii) antibiotics susceptibility tests. Antimicrobial susceptibility of isolates was tested by modified Kirby-Bauer disk diffusion method and inhibition zones were interpreted according to CLSI (Clinical and Laboratory Standards Institute) guidelines. Moreover, the methicillin-resistant test was also done [13-15].

Statistical Analysis

Categorical variables were expressed as several patients and percentage of patients and compared across the groups using Pearson's Chi-Square Test for Independence of Attributes. Continuous variables were expressed as Mean ± standard deviation and compared across the two groups using an unpaired t-test (SPSS version 20).

RESULTS

80 patients in each HIV negative (40 male and 40 female) and HIV positive (26 male and 54 female) groups were selected. The average age of HIV positive group was 44.95 yrs and HIV negative group was 41.45 yrs. There were significant variations in signs and symptoms were noted between the two groups. 7.5% of HIV-negative patients felt a burning sensation during micturition, while 15% experienced a burning sensation with fever, 34% had dysuria and 17.5% reported pain in loin. Though all these signs and symptoms were absent in HIV-positive patients, 95% of them excreted high-colored urine. Furthermore, 7.5% of HIV-negative patients were catheterized, while it was 20% in HIV-positive patients. There was no significant variation found in the number of days of hospitalization between these groups (Table 1). In urine samples, Gram-negative organisms were found in 85% of cases. 42.5% of HIV-negative and 22.5% of HIV-positive patients exhibited *E. coli* in their urine. Other microorganisms like *S. aureus* and *Enterococcus spp.,* were also found in both groups, but *Acinetobacter spp*., *Morganella morganii*, *Serratia marcescens*, *Staphylococcus epidermidis,* and *Citrobacter spp.,* were only existed in HIV positive patients (Table 2).

Antimicrobial sensitivity study showed Gram-negative isolates were multi-resistant to antibiotics in the following order: Ceftazidime>Tigecyclin>Vancomycin>Imipenrm>Polymixin (Figure 1).

Table 1 Clinical symptoms and demographic details of selected participants

	HIV-negative (Number/percent)	HIV-positive (Number/ percent)	p-value
Number of Patients	80	80	
Male	40 (50)	26 (32.5)	Not significant
Female	40 (50)	54 (67.5)	
Age (yrs.)	41.45 ± 18.24	44.95 ± 10.62	Not significant
Religion			
Hindu	44 (55)	50 (62.5)	Not significant
Muslim	36 (45)	30 (37.5)	
Education			
Illiterate	40 (50)	60 (75)	<0.001
Literate	40 (50)	20 (25)	
Clinical symptoms			
Burning sensation (maturation)	6 (7.5)	0 (0)	<0.001
Burning sensation (maturation and fever)	12 (15)	0 (0)	
Dysurea	34 (42.5)	2 (2.5)	
Frequently of maturation and fever	0 (0)	2 (2.5)	
Pain in loin	14 (17.5)	0 (0)	
Pain in loin and fever	14 (17.5)	0 (0)	
High colored urine	0 (0)	76 (95)	
Catheterized or not			
Not	74 (92.5)	64 (80)	<0.02
Yes	6 (7.5)	16 (20)	
Days of hospital stay	5.28 ± 1.84	5.35 ± 1.5	Not significant

Table 2 Frequency of different isolates present in NUTI patients

Isolates	HIV negative (Number/ percent)	HIV positive (Number/ percent)	p-value
Acinetobacter spp.	0 (0)	4 (5)	<0.02
Citrobactae frenduii	2 (2.5)	0 (0)	
E. coli	34 (42.5)	18 (22.5)	
Enterecoccus	12 (15)	14 (17.5)	
Enterobacter spp.	0 (0)	2 (2.5)	
Klebsiella oxytoca	4 (5)	6 (7.5)	
Klebsiella pneumonia	8 (10)	6 (7.5)	
Serratia marcescens	0 (0)	2 (2.5)	
Morganella morgannii	0 (0)	2 (2.5)	
Proteus mirabilis	4 (5)	8 (10)	
Pseudomonas aerugenosa	2 (2.5)	8 (10)	
Staphylococcus aureus	14 (17.5)	4 (5)	
staphylococcus epidermidis	0 (0)	4 (5)	
Ciyrobacter koserii	0 (0)	2 (2.5)	

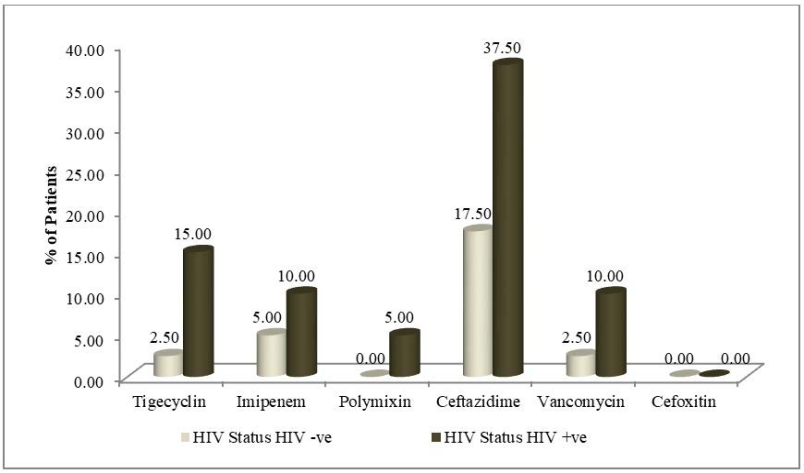

Figure 1 Antibiotics resistant pattern of NUTI patients suspect to various antibiotics

DISCUSSION

NUTI is becoming an important public health problem. The tragedy of this situation is that people are coming to the hospitals to get rid of their health-related problems, when they are acquiring another infection independent of their primary situation, exacerbating their existing ill-health. The organisms causing nosocomial infections can be transmitted to the community through discharged patients, staff, and visitors [9]. If organisms are multi-resistant, they may cause significant disease in the community. Nosocomial infections appear to be more fatal in HIV-positive individuals with AIDS as opposed to HIV-negative individuals. Nosocomial urinary tract and respiratory tract infections are also common in HIV-infected AIDS patients following bacterial colonization [16]. In the present study, the distribution and antibiotic susceptibility pattern of different bacteria isolated from both HIV+ and HIV- patients, who acquired UTI, at least 48 hr after being admitted to the hospital were focused. In this study, patients who were screened negative for urinary tract infections, at the time of hospital admission and converted to cultured positive with significant colony count, after 48 hr of hospital stay were only included.

The study included 80 patients in each group and there is no significant difference in age of the patients among HIV positive and HIV negative groups. Female preponderance was noted in HIV positive group, 67.5% were female. Although there was no significant association found between the distributions of religion, there was a difference between the literacy statuses of HIV positive group. A study conducted in Thailand by Kovavisarach, et al., showed subjects with lower education levels were acquiring more UTI than subjects with higher education levels [17]. Emiru, et al., observed similar findings in Ethiopia [18]. There was significant variation between the presenting symptoms of the two groups. Dysuria was the most frequent urinary symptom among the HIV-negative group (34%); while high coloured urine was noted in 95% of HIV-positive patients. Pain in loin, pain in loin with fever, burning sensation during maturation with fever were the important presenting symptoms among the HIV-negative group, found in this study, accounting for 17.5%, 18%, and 15% respectively. But strikingly the features were absent among HIV-positive groups. In HIV-positive patients presenting with dysuria were found only 2.5% of cases. Significant variation was observed between catheterization among these groups. In the case of HIV-negative patients, only 7.5% were catheterized, while it was 20% in the HIV-negative group. But, there was no significant variation found in the number of days of hospitalization between these groups.

Hospital environments are a significant determinant of the type of organisms causing UTI. The isolated Gram-negative organisms were found in 85% of cases, similar to earlier studies reported by Meher Rizvi and his colleagues [19]. *Escherichia coli* had topped the list of bacterial isolates among both the groups in this study. *E. coli* were isolated from 42.5% of urinary samples of HIV-negative NUTI patients and 22.5% samples of HIV-positive. Moreover, *S. aureus* was isolated in 17.5% of HIV-negative patients, similar to the observation of Okonko, et al. [20]. Furthermore, it was observed *Enterococcus* species in 10% of samples of HIV-positive UTI infected patients. A previous report from Ethiopia has supported a similar type of observation [21]. Another study conducted in a rural health centre in Nigeria

depicted *E. coli* as the predominant uropathogen, which is the same as the present one, but differing in the second most common pathogen as *Staphylococcus aureus* instead of being *Enterococcus* species [22]. Therefore, it can presume that different geographical areas have different microbial reservoirs.

There were significant differences between recovered isolates among the two groups. *Acinetobacter spp.*, *Morganella morganii*, *Serratia marcescens,* and *Staphylococcus epidermidis* were missing from the urinary isolates of HIV-negative patients, while they were observed in HIV-positive patients. Interestingly, *Serratia marcescens* has been newly identified in the host institution as a urinary tract pathogen. *Morganella morganii* was found in 2.5% of cases of HIV-positive patients suffering from UTI. Coagulase Negative *Staphylococci* (CONS) had been considered an important urinary pathogen in different kinds of literature. But most strikingly, CONS has been missing from the present study among the urinary isolates of HIV-negative patients. Perhaps, *Citrobacter* spp, particularly *Citrobacter frenduii* was found in 2.5% of isolates among HIV negative group, while, *Citrobacter koserii* was found in 2.5% of isolates among HIV positive group.

Antimicrobial therapy is effective and therapeutic guidelines are based on local antibiotic susceptibility patterns. However, antimicrobial drugs may either cure the infection or may cause bacterial persistence, relapse, or re-infection. Ampicillin, amoxicillin-clavulanic acid, cefuroxime, cefotaxime, ceftazidime, ceftazidime-clavulanic acid, cefepime, imipenem, trimethoprim-sulphamethoxazole, nitrofurantoin, levofloxacin, amikacin, and gentamicin were used for isolates of the *Enterobacteriaceae* family and other gram-negative organisms to find out the antimicrobial sensitivity. Irrespective of the HIV status, Gram-negative isolates were very much resistant to Ampicillin and amoxicillin-clavulanic acid. Moreover, cefuroxime, cefotaxime, and ceftazidime were highly resistant among *E. coli* as well as other Gram-negative isolates. According to the WHO Global Report on surveillance, antimicrobial resistance is increasing in the South Asian and African regions. There have also been reports of a significant number of antimicrobial-resistant bacteria that are transmissible in hospitals and communities [23-25]. In this study, nitrofurantoin resistance was high among urinary isolates. Fluoroquinolone resistance was also high among the isolates. Most of the isolates especially *Pseudomonas aeruginosa* were highly sensitive to the Piperacillin-Tazobactam (PIT) combination. Imipenem has also shown high sensitivity among different Gram-negative isolates. Polymixin b, tigecycline, and colistin were also found highly sensitive among Gram-negative isolates. Furthermore, various unusual isolates have been recovered from HIV-positive patients. This was probably the reflection of a vulnerable immune system, making HIV-positive patients susceptible to organisms generally considered non-pathogenic. But regarding antimicrobial susceptibility, all the organisms were highly resistant, irrespective of the HIV status of the patients, from whom they were isolated.

In contrast to Gram-negative isolates, all Gram-positive isolates were sensitive to first and second-line drugs. Among the total isolates thirteen were *Enterococcus* spp. and eleven were *S. aureus*. Interestingly, all of the isolates of *S. aureus* were cefoxitin sensitive, which is an unusual and new finding. A study done by Robert and his colleagues in Pennsylvania found 83% of *S. aureus* isolated from patients acquiring NUTI were methicillin-resistant [26]. Previous studies have shown that an increase in these bloodstream infections is associated with HIV infections [27]. Hence, if gram-positive isolates are recovered, the clinicians can be advised to keep third-generation antibiotics in reserve and can start empirical regimen undoubtedly with first-line drugs, avoiding unnecessary misuse of higher antibiotics.

CONCLUSION

Nosocomial infection, particularly UTI is a serious problem that is continually increasing and produces a severe threat. In immunocompromised HIV-infected patients, this threat is further amplified. Therefore, we can conclude that as antibiotic stewardship is a concern in NUTI, clinicians and microbiologists have to work as a team.

DECLARATIONS

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Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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