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STUDY OF ANTIBIOTIC SENSITIVITY OF *STAPHYLOCOCCUS AUREUS* AS A CAUSE OF URINARY TRACT INFECTION IN A TERTIARY CARE HOSPITAL IN CENTRAL INDIA

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ABSTRACT

Background: *Staphylococcus aureus* is a relatively uncommon cause of urinary tract infection in the general population. However, recent epidemiologic studies indicate that *S. aureus* is an emerging cause of UTI in special patient populations, such as pregnant women and those with complicated UTI. Of particular concern, complicated *S. aureus* UTIs are frequently associated with the development of severe sequelae, leading to increased rates of morbidity and mortality. **Material and methods:** *Staphylococcus aureus* isolates obtained from various urine samples were studied from January 2015 to October 2017 in the Microbiology Diagnostic Laboratory for their antibiotic sensitivity and co-morbidities. **Results:** A total of 2590 urine culture positive samples were received in Diagnostic Microbiology Laboratory during the study period. Out of these *S. aureus* was found in 69 samples. (2.66%). Out of these 69 urine samples, 31(56.52%) were from Catherized and 38(50.72%) from non-Catheterized patients. Out of 69 samples 57 (82.60%) patients had some or the other co-morbidities such as Diabetes, Hypertension, post menopausal females, pregnant females etc. Antibiotic sensitivity testing was done for all *S.aureus* isolates. Highest antibiotic sensitivity was seen towards Vancomycin and Pristinamycin(100%). Least sensitivity was seen towards Penicillin G in both MRSA and MSSA isolates. **Conclusion:** Urinary tract infections caused by multi drug resistant *S.aureus* is an emerging problem in hospitals. infection control practices play a vital role in controlling these life threatening infections. Vancomycin, cotrimoxazole and nitrofurantoin are good options for empirical treatment of MRSA UTIs. Pristinamycin is also a good option for treating UTI caused by MRSA.

KEYWORDS: *Staphylococcus aureus,* Urinary tract infections, Antibiotic sensitivity.

INTRODUCTION

Staphylococcus aureus is a relatively uncommon cause of urinary tract infection in the general population.[1,2] *Staphylococcus aureus* bacteriuria is suspected to occur through a limited number of mechanisms--primarily ascending spread after instrumentation (e.g., urologic procedures or urethral catheterization) or hematogenous seeding of the genitourinary tract. Urinary tract instrumentation and the presence of an indwelling catheter increase the risk of *S. aureus* carriage in the urinary tract.[1,3]

The majority of cases of *S. aureus* bacteriuria are not associated with symptoms of urinary tract infection.[1] Because bacteriuria nearly universally occurs concomitantly with long-term urinary catheterizationthe clinical significance of isolation of *S. aureus* from the urine is undefined in such patients.[4,5] Although urinary *S. aureus* may be the source of staphylococcal bacteremia, the proportion of patients with chronic *S. aureus* bacteriuria who subsequently become bacteremic is unknown.[6,7,8]

As *Staphylococcus aureus* only accounts for between 0.5 and 2% of all urine positive cultures, the gram-positive pathogen is not typically considered a major cause of urinary tract infection (UTI).[9,10,11] However, recent epidemiologic studies indicate that *S. aureus* is an emerging cause of UTI in special patient populations, such as pregnant women and those with complicated UTI.[12-18]

Of particular concern, complicated *S. aureus* UTIs are frequently associated with the development of severe sequelae, leading to increased rates of morbidity and mortality.[12,14,16-21]

Additionally, treatment of these infections has become increasingly difficult, as most *S. aureus* isolates causing complicated UTI are methicillin resistant *S. aureus*

(MRSA) and are refractory to treatment by antibiotics that typically have efficacy in the urinary tract.[12,16,22,23]

This highlights the need for developing a greater understanding of the pathogenesis of complicated UTI for the development of new antibiotic-sparing therapies.

AIM

To study the underlying co-morbid conditions of patients and antibiotic sensitivity pattern of *S.aureus* in urine samples of patients suffering from Urinary tract infections.

OBJECTIVES

1. To isolate *S.aureus* from urine samples of patients suffering from Urinary tract infections.
2. To identify the various underlying co-morbid conditions.
3. To study the antibiotic sensitivity pattern of *S.aureus* in these patients.
4. To study methicillin resistance among *S. aureus* isolates.
5. To study inducible and constitutive clindamycin resistance among *S. aureus* isolates.
6. To study the susceptibility of glycopeptide (Vancomycin) amongst MRSA isolates.

MATERIAL AND METHODS

A hospital based cross sectional study was carried out from January 2015 to October 2017 in the Microbiology Diagnostic Laboratory of Government Medical College, Nagpur. The study was approved by the Institutional Ethical Committee.

Sample size was calculated by the statistician using standard guidelines, as per the public service of creative research systems survey software.

Staphylococcus aureus isolates obtained from various urine samples received in Microbiology Diagnostic Laboratory at Government Medical College, Nagpur for the microbiological investigations were selected for the study.

The quality control and rejection criteria for the in-appropriate specimens were followed as per the standard guidelines.[24]

Specimens were processed within 2 hours of collection by the standard microbiological technique.[24]

Sample collection

Mid stream urine samples were collected from adult and in pediatric patients, either mid stream urine or urine from a sterile bag in infants were collected. Male Patients were instructed to clean their penile area with soap and water and retract the foreskin of glans before collecting mid stream urine samples. Female patients were instructed to clean their perineal area with soap and water and then separate their labia before collecting mid stream urine samples.

For collection of urine from catherized patients, sample was collected by sterile needle and syringe by puncturing the catheter in upper $1/3^{rd}$ part after cleaning it with 70% alcohol.[25]

Screening test

Microscopic examination of all uncentrifuged urine samples was done. Presence of pus cells and cocci was noted.

Culture of urine samples

All the urine samples were plated on sheep Blood agar and Mac Conkey agar (Hi Media). A calibrated loop of 0.01ml was used for colony count. After delivering the inoculums from the calibrated loop, the surface of each agar plate was streaked completely over all quadrants so that semi quantitative colony counts can be performed after incubation. A colony count of 10^5 was the criterion most commonly used for significant bacteriuria, but for *S.aureus* 10^3 or more was considered significant. Even lower colony counts were considered significant in females with acute urethral syndrome.[25]

Diagnosis of Urinary tract infection was made on combined approach of evaluating clinical symptoms, microscopy and culture report.

Isolation

Specimens showing pus cells with Gram positive cocci in clusters in primary smear were given special attention. The plates were then incubated at 35 ± 2^0 Celsius for 18 - 24 hours in aerobic atmosphere.[24]

Identification of genus staphylococcus

After the plates were examined, any colony showing morphology suggestive of Staphylococcus, showing beta-haemolysis / no haemolysis, butyrous in consistency on blood agar plates were studied by Gram stain.

Gram positive cocci uniform in size, appearing characteristically in groups mostly, but also seen singly and in pairs were further identifed by the scheme described for the identifcation of the gram positive cocci arranged in clusters using following tests.[24]

Catalase test, Modified Oxidase test, Furazolidone susceptibility test, Coagulase test(slide and tube coagulase), Mannitol sugar fermentation test.[24]

Antimicrobial susceptibility testing was performed as per the CLSI guidelines (2017) by modifed Kirby Bauer method.[26,27]

Antibiotic discs

Commercially available antibiotic discs (Hi-media laboratories Pvt.Ltd. Mumbai) with proper diameter and potency were used. All the strains were tested for their

sensitivity to antimicrobial drugs using recommended CLSI guidelines (2017) combined with institutional antibiotic policy and hospital formulary practices for the purpose of reporting to the clinician.[26]

Zone Diameter Interpretation Standards in mm (CLSI 2017)

Sr. No	Name of Drug & Symbol	Conc. Of Drug	Sensitive (mm)	Intermediate (mm)	Resistant (mm)
1	Penicillin G (P)	10 units	≥29	-	≤28
2	Cotrimoxazole(COT)	1.25 / 23.75 µg	≥16	11-15	≤10
4	Cefoxitin (CX)	30 µg	≥22	-	≤21
5	Ciprofloxacin (CF)	5 µg	≥21	16-20	≤15
6	Ofloxacin(OF)	5 µg	≥18	15-17	≤14
7	Tetracycline (T)	30 µg	≥19	15-18	≤14
8	Gentamicin (G)	10 µg	≥15	13-14	≤12
9	Norfloxacin (NX)	10 µg	≥17	13-16	≤12
10	Erythromycin (E)	15 µg	≥23	14-22	≤13
11	Clindamycin (CD)	2 µg	≥21	15-20	≤14
12	Linezolid (LZ)	30 µg	≥ 21	-	≤ 20
13	Pristinamycin (PM)	15 µg	≥ 19	16-18	≤ 15
14	Nitrofurantoin(NF)	300 µg	≥ 17	15-16	≤14

MRSA detection (Methicillin Resistant *S. aureus*)

In this study, MRSA detection was performed by cefoxitin disk diffusion method.

Cefoxitin disk diffusion testing[28]

All the *S. aureus* isolates were subjected to cefoxitin disk diffusion test using a 30 µg disk. A 0.5 McFarland standard suspension of the isolate was prepared and lawn culture done on Mueller–Hinton Agar plates with 4% NaCl.

Plates were incubated at 37^0 C for 18 hour and zone diameters were measured.

A zone size of ≥22mm was considered sensitive, ≤ 21mm was considered resistant.

RESULTS

A total of 2590 urine culture positive samples were received in Diagnostic Microbiology Laboratory during the study period. Out of these *S. aureus* was found in 69 samples. (2.66%).

Table number 1: Total number of Adult and Pediatric patients (n=69).

Sr. No	Patients	Total number
1.	Adults	56(81.15%)
2.	Pediatric patients	13(18.84%)
3.	**Total**	**69(100%)**

Out of these 69 urine samples, 56 samples were from adults (81.15%) and 13 samples were from pediatric patients (18.84%).

Table number 2: Total number of Males and Females (n=69).

Sr. No	Sex	Total number
1.	Males	14(20.28%)
2.	Females	55 (79.71%)
3.	**Total**	**69(100%)**

Out of these 69 urine samples, 55 (79.71%) were female patients and 14(20.28%) were male patients.

Table number 3: Total number of Catherized and non-Catheterized patients (n=69).

Sr. No	Type of patients	Total number
1.	Catherized	31(56.52%)
2.	Non-Catheterized patients	38(50.72%)
3.	**Total**	**69(100%)**

Out of these 69 urine samples, 31(56.52%) were from Catherized and 38(50.72%) from non-Catheterized patients.

Table number 4: Sex wise distribution of Catherized patients (n=31).

Sr. No	Sex	Number
1.	Males	5(16.12%)
2.	Females	26(83.87%)
3.	**Total**	**31(100%)**

Out of the 31 patients, only 5(16.82%) were from male patients while rest of the 26 (83.87%) were from female patients.

Table number 5: Age-wise distribution of Catherized patients(n=31).

Sr. No	Age –wise distribution	Number
1.	Adults	3(9.67%)
2.	Pediatric patients	28 (90.32%)
3.	**Total**	**31(100%)**

In these 31 patients only 3(9.67%) were from pediatric patients while rest 28 (90.32%) were adults.

Table number 6: Co-morbid conditions of patients suffering from Urinary tract infection due to *S.aureus* (n=57).

Sr. No	Co-morbid condition	Total Number (%)
1.	Urinary tract instrumentation or obstruction	17(29.82%)
2.	Genito-urinary tract surgery	16(28.07%)
3.	Diabetes	10(17.54%)
4.	Hypertension	3(5.26%)
5.	Post menopausal females	4(7.01%)
6.	Pregnant females	5(8.77%)
7.	Other	2(3.50%)
	Total	**57(100%)**

Co- morbidities

Out of 69 samples 57 (82.60%)patients had some or the other co-morbidities such as Diabetes, Hypertension, post menopausal females, pregnant females etc.

The remaining 12 patients had no co-morbid conditions.

Table number 7: Detection of Methicillin resistant *S. aureus* (MRSA) by cefoxitin (30ug) disk using Kirby Bauer method (n=69).

Cefoxitin (30ug) disk diffusion	Resistant
MRSA (Methicillin resistant *S. aureus*)	29(42.02%)
MSSA(Methicillin Sensitive *S. aureus)*	40(57.97%)
Total	**69(100%)**

Out of the total number of isolates, 42.02% were MRSA.

Table number 8: Antimicrobial susceptibility pattern of Methicillin Sensitive *S.aureus (*MSSA) by disk diffusion method (n=40).

Sr. No	Antibiotics	Sensitive no (%)	Resistant no (%)
1	Penicillin G (P)	Nil(%)	(100%)
2	Cotrimoxazole(COT)	39(97.5%)	1(2.5%)
3	Ciprofloxacin (CF)	34 (85%)	6(15%)
4	Ofloxacin(OF)	29(72.5%)	11(27.5%)
5	Tetracycline (T)	32(80%)	8(20%)
6	Gentamicin (G)	39(97.5%)	1(2.5%)
7	Norfloxacin	36(90%)	4(10%)
8	Linezolid (LZ)	40(100%)	0(0%)
9	Pristinamycin (PM)	40(100%)	0(0%)
10	Nitrofurantoin(NF)	34(85%)	6(16%)
11	Vancomycin (E-Strip)	34(100%)	0(0%)

The highest sensitivity was seen towards Vancomycin and Pristinamycin (100%) and least sensitivity was seen towards Penicillin G.(0%)

Table No 9: Antibiotic sensitivity pattern of various antibiotics to all Methicillin resistant *S. aureus* (MRSA) isolates (n=29).

Sr. No	Antibiotic	Sensitive no (%)	Resistant no (%)
1	Penicillin G (P)	0(0%)	29(100%)
2	Cotrimoxazole(COT)	16(55.17%)	13(44.82%)
3	Ciprofloxacin (CF)	9(31.03%)	20(68.96%)
4	Ofloxacin(OF)	4(13.79%)	25(86.20%)
5	Tetracycline (T)	14(48.27%)	15(51.72%)
6	Gentamicin (G)	15(51.72%)	14(48.27%)
7	Norfloxacin	10(34.58%)	19(65.51%)
8	Linezolid (LZ)	29(0%)	0(0%)
9	Pristinamycin (PM)	29(100%)	0(0%)
10	Nitrofurantoin(NF)	19(65.51%)	10(34.48%)
11	Vancomycin (E-Strip)	34(100%)	0(0%)

The highest sensitivity was seen towards Vancomycin and Pristinamycin (100%) and least sensitivity was seen towards Penicillin G.(0%)

Table 10: Comparison of different types of MLS_B resistance among *S. aureus* on D-zone test.

Phenotype Susceptibility pattern	MRSA (%) (n=29)	MSSA (%) (n=40)
Inducible Clindamycin resistance (MLS_Bi) (ER-R, CL-S, D test +ve)	7(24.13%)	8(20%)
Constitutive Clindamycin resistance (MLS_Bc) (ER-R, CL-R)	11(37.93%)	11(27.5%)
MS Phenotype (ER-R, CL-S, D test -ve)	8(27.58%)	8(20%)
Susceptible to Erythromycin & Clindamycin (ER-S, CL-S)	3(10.34%)	13(32.5%)

DISCUSSION

S. aureus is a relatively infrequent urinary tract isolate in the general population. In a multicenter, community-based study conducted in Great Britain, *S. aureus* accounted for only 0.5% of isolates.[29] A similar laboratory-based study conducted in France found that *S. aureus* accounted for only 1.3% of isolates from urine specimens submitted from the community.[30]

Prior studies suggest that isolation of *S. aureus* from the urine is often secondary to staphylococcal bacteremia originating at another site (e.g., in cases of endocarditis).[31] In specific patient populations, however, *S. aureus* can be an important primary urinary pathogen. There is evidence that *S. aureus* is a primary urinary tract pathogen in this population. Using the CDC criteria for nosocomial infection to define urinary tract infection, researchers found that 4% of cases of bacteremia of urinary tract origin among long-term care patients were due to *S. aureus.*[32]

In our study, we encountered a total of 42% MRSA isolates.

Till here

Age and sex wise distribution of patients

In our study, we found that adults (81.15%) were always at a higher risk than children (18.84%) to acquiring UTI. Similarly females (83.87%) were at a higher risk of contracting the illness due to various reasons like shorter urethra, pregnancy, post menopausal state etc.

Researchers have illustrated the prevalence of pathogen among the elderly patients as a consequence of catheters and this rules out the condition of bacteriuria due to UTI. Nevertheless prolonged use of indwelling catheters can result in UTI, but a clear differentiation between the asymptomatic bacteriuria and UTI among elderly patients is yet to be understood.[33,34]

Co-morbid conditions

Various co-morbid conditions also play an important role in causing UTI like catheterization (56.52%) which was the highest followed by Urinary tract instrumentation or obstruction (29.82%). Genito-urinary tract surgery (28.07%), Diabetes (17.54%).

Pregnancy accounted for 8.77% of infections. However, recent epidemiologic studies indicate that *S. aureus* is an emerging cause of UTI in special patient populations, such as pregnant women and those with complicated UTI.[12-18]

Several demonstrative studies have claimed the role of *S. aureus* in conferring UTI among women and pregnancy is considered as a crucial period which enhances the scope of the infection. UTI during pregnancy can lead to consequences like Perinatal and maternal morbidity and mortality in turn complicating pregnancy. The nature of infection can either be symptomatic leading to cystitis or pyelonephritis or the infection could be asymptomatic where the patient does not show any clinical symptoms. The significance of UTI and its association with perinatal complexities has been illustrated by several studies.[35,36] The occurrence of UTI among women during pregnancy ranges from 2-10% globally.[37,38]

Researchers regard *S. aureus* as an opportunistic pathogen that is capable of influencing the immune competent and immune compromised individuals as the pathogen is known to compromise an individual's immune system. This is one of the reasons that patients after surgery are prone to *S. aureus* infection.[39] In addition to surgical patients, new born babies and patients with diabetic history are highly prone to *S. aureus* infection.[40,41]

Antimicrobial susceptibility pattern of Methicillin Sensitive *S.aureus (*MSSA) by disk diffusion method.

The highest sensitivity was seen towards Vancomycin and Pristinamycin (100%) followed by Cotrimoxazole and Gentamycin (97.5%), Nitrofurantoin accounted for 85% sensitivity. No sensitivity was seen towards Penicillin (0%) The reason for this type of sensitivity may be over and indiscriminate use of other antibiotics in various types of hospital settings.

Antibiotic sensitivity pattern of various antibiotics to all Methicillin resistant *S. aureus* (MRSA) isolates

Methicillin resistant strains of *S. aureus* is clinically significant and has gained the attentions of global scientific researchers due to the fact that a single genetic element offers resistance against the beta lactam antibiotics like penicillin, cephalosporins, carbapenems. Due to the rapid rise of MRSA isolates, vancomycin is used as the first line drug for treating the patients. This constant administration of the drug among the hospitalized patients has reduced the potency of the drugs against the MRSA.[42]

The highest sensitivity in our study was seen towards Vancomycin and Pristinamycin (100%) followed by Nitrofurantoin (65.51%) and Cotrimoxazole (55.17%)]. No Vancomycin resistant strain was encountered.

According to our study, Vancomycin and nitrofurantoin are good options in MRSA urinary tract infections.

Several demonstrative studies have validated the existence of MRSA as a consequence of constant exposure to health care centers and long term hospitalized condition among patients is prone to such infections.[43,44]

Many demonstrative studies have validated the existence of MRSA as a consequence of constant exposure to health care centers and long term hospitalized condition among patients is prone to such infections. The most significant risk factor for developing complicated MRSA UTI is urinary catheterization.[12,16,17,20] Recent studies have highlighted that in contrast to catheter-associated UTI(CAUTI) caused by other bacteria, MRSA dissemination to bacteremia following bacteriuria occurs more frequently (5 vs. 20%, respectively) and manifests rapidly, typically within 2 days of a urine positive culture.[16,20]

CONCLUSION

Urinary tract infections caused by multi drug resistant *S.aureus* is an emerging problem in hospitals. Because urinary catheterization is a major risk factor for *S.aureus* bacteriuria, reducing the infections caused by urinary catheterization is to be taken care of. Increasing hospital infection control practices play a vital role in controlling these life threatening infections. Antibiotic sensitivity pattern of *S.aureus* in these infections need to be studied in detail to initiate and continue appropriate antibiotic drugs. Vancomycin, cotrimoxazole and nitrofurantoin are good options for empirical treatment of MRSA UTIs. Pristinamycin is also a good option for treating UTI caused by MRSA.

Conflict of interest –Nil.

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