Antibiotic Susceptibility Profile of *Staphylococcus Saprophyticus* Cause Urinary Tract Infection in Tertiary Care Hospital Peshawar

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Abstract

Staphylococcus saprophyticus (*S. saprophyticus*) *is the second most constant acute agent of urinary tract infections (UTIs) mostly in young females. The study aimed to determine the prevalence, antibiotic susceptibility profiles, MDR pattern, and resistance to various classes of antibiotics of S. saprophyticus in patients coming to tertiary care hospitals. A total of 475 clinical isolates were collected and initially confirmed by Gram staining and further confirmation was done through Standard Microbiological Procedures. Generally, S. saprophyticus was identified by novobiocin resistance, absence of hemolysis, and by Remel RapID™ Staph Plus System. Antibiogram was done using the Kirby Bauer Disk Diffusion method. Results interpretation was done using the Clinical & Laboratory Standards Institute (CLSI) (2021) guidelines. Overall, out of 475 isolates 375 were coagulase-negative and 100 were coagulase-positive, out of coagulase-negative 164 were confirmed as S. saprophyticus in which females were dominant as compared to males. while the rest were confirmed as other coagulase-negative staphylococci. Urine was the main sample source. The highest resistance to tobramycin (91%), followed by ofloxacin (85%), penicillin G (91%), and erythromycin (67%) was observed respectively. The highest sensitivity was noticed to vancomycin (92%), gentamicin (57%), and oxacillin*

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(44%). About 96.3% of the isolates were termed as multi-drug resistant (MDR). The highest resistant to various class of antibiotic that showed resistance to erythromycin, gentamycin, levofloxacin, ofloxacin, oxacillin, penicillin, tobramycin, and amoxicillin with a percent prevalence of 15%. There is no association found between the two variables i.e. antibiotic susceptibility pattern of S. saprophyticus and gender. The high prevalence of MDR and resistance to various classes of antibiotics among S. saprophyticus pose a challenge for clinicians and public health experts which needs to be investigated.

Keywords: S. saprophyticus, Novobiocin Resistance, Remel RapID^{TM} Staph Plus System, MDR.

Introduction

Staphylococci is a group of Gram-Positive bacteria divided into Coagulase positive and Coagulase negative bacteria. *Staphylococcus aureus* (*S. aureus*) is nowadays an emerging and growing problem in our society and hospital. Generally, we use antibiotics against every bacterium involved in infection. But some exceptional bacteria show resistance to that antibiotic (Tokajian, 2014). Urinary Tract Infections (UTIs) are among the most occurring infection around 150-250 million cases globally per year (Zowawi et al., 2015). So, one of the species of staphylococci is *S. saprophyticus* a Gram-positive bacterium, usually the causative agent of UTIs, which especially occurs in young sexually active females (Argemi et al., 2019). As, we know that *S. aureus* is the normal flora present in the nose (temporarily) of about 30% of healthy persons and about 20% on the skin (Larry, 2021). Usually, the percentage was observed higher in those people who are already admitted to hospitals and those who are working there (Hussain et al., 1986).

S. saprophyticus is the 2nd most occurring acute agent of our community-acquired UTIs after *Escherichia coli* (*E. coli*) (E.W.Konemann et al., 2001). It shows resistance to those antibiotics which are commonly used against UTIs caused by *E. coli* including ampicillin, ceftriaxone, cephalexin, and ciprofloxacin. *S. saprophyticus* was generally recognized by novobiocin resistance (Ehlers & Merrill, 2018), the absence of hemolysis, and using biochemical tests including tube coagulase and DNase, etc. The simplified battery system of biochemical tests introduced by Cunha et al, (2004) is a new identification key for *S. saprophyticus*. Generally in UTIs infection, the pathogenicity of other coagulase-negative staphylococci (CONs) is indecisive, but the clinical importance of (*S. haemolyticus*, *S. epidermidis*, *S. simulans*, *S. sciuri*, *S. capitis*, *S. xylosus*, *S. warneri*, *S. cohnii*, *S. lentus*, and *S. hominis*) was revealed (Guirguitzova, Chankova & Zozikov, 2002 and Alcaráz et al., 2003).

A study from Kohat showed that *S. saprophyticus* isolates were resistant to ceftriaxone (50%) followed by ceftazidime (100%), cefepime (16.7%), and ciprofloxacin (66.7%), respectively (Ullah, Shah, Almugadam & Sadiqui, 2018). Another study from our neighboring country like India showed sensitivity in *S. saprophyticus* against co-trimoxazole (90%), while 80% of isolates to nalidixic acid, clindamycin, and vancomycin respectively (Sibi, Kumari, & Kabungulundabungi, 2014). The current study aimed to find out the UTIs mainly in sexually active women caused by *S. saprophyticus*, their antibiotic susceptibility profiles, and the MDR pattern as well as their resistance phenotypes circulating in our local clinical settings.

Methods

Sample collection

The present study was cross-sectional. The duration of the study was from February 2022 to August 2022. A total of 475 staphylococci clinical isolates were collected aseptically from midstream clean-catch urine by standards procedures mainly from the patients based on gender and age having UTI infection at Hayatabad Medical Complex Peshawar. Growth characteristics were observed on mannitol salt agar (MSA) medium and further re-confirmation was done by a series of biochemical tests such as DNase, tube coagulase, and the absence of hemolysin production. Moreover, its identification was done by using Remel RapID^{TM} Staph Plus System.

Antibiotic Susceptibility Testing

A panel of antibiotics was applied using the Kirby Bauer Disk Diffusion method (Bauer, 1966) i.e. erythromycin (15µg), gentamicin (10µg), levofloxacin (5µg), ofloxacin (5µg), oxacillin (1µg), penicillin (10 units), vancomycin (30µg), tobramycin (10µg), amoxicillin + clavulanic acid (20/10µg) (Oxoid, UK). All the results were interpreted according to the Clinical and Laboratory Standard Institute (CLSI) 30 edition 2020.

Multidrug Resistant (MDR) Criteria

The phenomenon is used when an organism (bacteria) shows resistance to three or more antimicrobial classes of bacteria (Cohen et al., 2008 & Pillar et al., 2008).

Resistance to various classes of antibiotics

All the confirmed study isolates were further analyzed for the resistance pattern to various classes of antibiotics.

Statistical Analysis

Statistical analysis was done using IBM SPSS 20.0 version.

Results

Patient Demographic Details

Overall, out of 475 staphylococci isolates of which 100 were confirmed as coagulase positive 375 were coagulase-negative, and out of coagulase-negative 164 were *S. saprophyticus*. The main sample source was urine (Figure 1 (c). The study isolates were also arranged based on wards, gender as well as age groups. The samples were mainly found with greater percentages in General Medicine and urology ward (Figure 1 (B), gender wise we found that 70% of females were affected while males had 30%, which shows that females are more prevalent to *S. saprophyticus* UTI infections as compared to males as shown in Figure 1(D). Age-wise distribution in patients of different age categories having variation in the prevalence of *S. saprophyticus* like specimens aged 21-30 years have the highest rate of infection at about 57%, specimens aged 11-20 years have infection about 38%, and the rest of the results were shown in (Figure 1 (A) respectively.

Antibiotic Susceptibility Assay

Isolates showed the highest resistivity against tobramycin (91%) following ofloxacin (85%) and penicillin (91%) respectively. While the highest sensitivity level to vancomycin (92%) follows oxacillin (44%) and the rest of the results were shown in Figure 2.

Prevalence of MDR Saprophyticus isolates

As we know that those bacteria which are resistant to three more than three antibiotics were named MDR. In this study, overall (n=158, 96.3%) *S. saprophyticus* isolates were MDR.

Association of Antibiotic resistance with gender

Our null hypothesis was the association of all antibiotics used in our study i.e. erythromycin, gentamycin, levofloxacin, ofloxacin, oxacillin, vancomycin, penicillin, tobramycin and amoxicillin + clavulanic acid with gender (male and female) statistically using SPSS and we get all our results nonsignificant (P-*value* >0.05). Thus, there is no association found between these two variables, results were shown below in Table 1.

Resistance to various classes of antibiotics

In the case of the resistant phenotypes of the study isolates, it was observed that 24 isolates were found to be resistant to 8 different classes of antibiotics i.e. erythromycin, gentamicin, levofloxacin, ofloxacin, oxacillin, penicillin-g, tobramycin, and amoxicillin +

clavulanic acid, followed by 11 isolates were found to be resistant to 7 different class of antibiotics i.e. erythromycin, gentamicin, levofloxacin, ofloxacin, oxacillin, and tobramycin, while the rest of the result as shown in Table 2 and Figure 3.

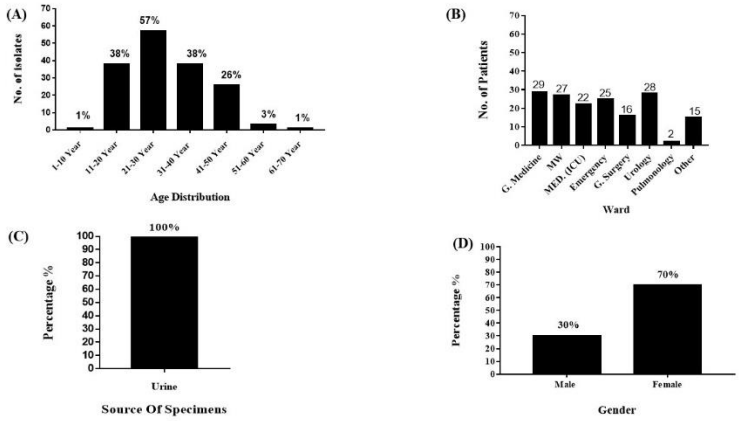

Figure 1: *S. saprophyticus* distribution according to specimen, gender, ward, and age (A) Age-wise distribution of isolates in different age groups (seven groups) (B) *S. saprophyticus* isolates from different wards of the hospital (C) Distribution of *S. saprophyticus* isolates based on the specimen (D) Gender wise distribution of study isolates of *S. saprophyticus.*

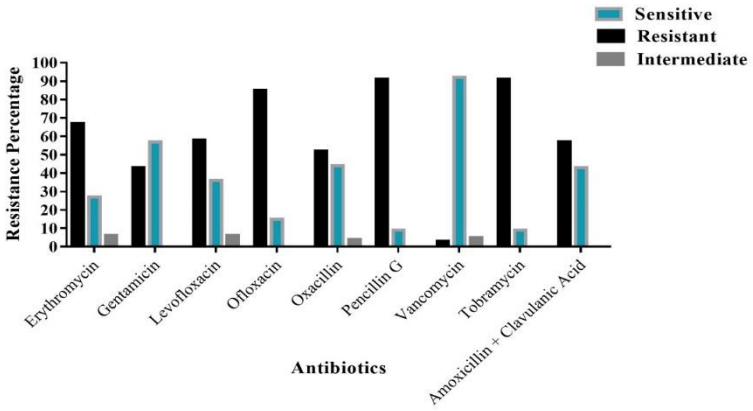

Figure 2: Antibiotic susceptibility profiles of the study isolates using GraphPad Prism 7.0.

Discussion

Urinary tract infections (UTIs) are one of the most prevalent infections globally having a growing trend in the ineffectiveness of antimicrobial therapies due to increased resistance. According to the best of our knowledge, we are reporting for the first time the occurrence of resistance phenotypes in clinical *S. saprophyticus*

isolates collected from tertiary care hospital in Peshawar, Pakistan. This resistance to various classes of antibiotics encourages the clinician to treat MDR *S. saprophyticus* isolates involved in complicated UTI infections.

In the current study, we focused on *S. saprophyticus* isolates that are more prevalent in the case of UTIs as the overall prevalence of *S. saprophyticus* is about 34% while another previous study from Baluchistan, Pakistan reported about 22.18% of cases that is the second most abundant cause of Uro pathogen after *E. coli* (Hussain et al., 2021). The infections are more common in women than men having a ratio of 7:3 respectively. Uropathogenic *E. coli* are responsible for more than 50- 90% of UTIs among all age groups. A recent report from Punjab Pakistan reported that coagulase-negative staphylococci (CoNS) with a percent prevalence of 3% (Idrees et al., 2022) involved in UTIs have been noticed. As compared to the previous study from Tehran where they found *E. coli* more prevalent in UTIs (Jarsiah et al., 2014). Another report from Turkey describes that *S. saprophyticus* was the second-most prevalent organism in 0.5% of isolates mainly from Urine specimens (Gul & Gurbuz, 2020), and 19.9% percent in Bangladesh (Haque, Akter & Salam, 2015), while a study from Northwest Ethiopia reported the prevalence of *S. saprophyticus* in 33.3% (Zerefaw, Tadesse & Derbie, 2022) all reports showed variation with the current findings. While a study from Iran reported a less percentage of *S. saprophyticus* at 1% (Bol, Iida & Mostafa, 2019). The variation in the prevalence of *S. saprophyticus* in various studies from Pakistan and other countries with the current study may be due to the number of isolates, the date of collection of isolates, the target organism, or may the geographical location.

Table 1

Showed the association of antibiotic susceptibility pattern with gender.

Variable	Erythromycin				P-value	Gentamycin				P-value	Amoxicillin				P-value
	R	I	S	Total		R	I	S	Total		R	I	S	Total	
Male	42	3	22	67	0.419	27	0	40	67	0.702	36	0	31	67	0.337
Female	68	6	23	97		42	0	55	97		58	0	39	97	
Grand Total	110	9	45	164		69	0	95	164		94	0	70	164	

Variable	Levofloxacin				P-value	Ofloxacin				P-value	Oxacillin				P-value
	R	I	S	Total		R	I	S	Total		R	I	S	Total	
Male	36	7	24	67	0.145	56	0	11	67	0.591	35	0	32	67	0.104
Female	59	3	35	97		84	0	13	97		51	6	40	97	
Grand Total	95	10	59	164		140	0	24	164		86	6	72	164	

Variable	Penicillin-G				P-value	Vancomycin				P-value	Tobramycin				P-value
	R	I	S	Total		R	I	S	Total		R	I	S	Total	
Male	62	0	5	67	0.683	3	3	61	67	0.243	60	0	7	67	0.467
Female	88	0	9	97		2	1	94	97		90	0	7	97	
Grand Total	150	0	14	164		5	4	155	164		150	0	14	164	

***Note:** R= Resistance, I= Intermediate, S= Sensitive*

P-Value = <0.05 (Significant) and P-Value = >0.05(Nonsignificant)

Table 2
Showed the antibiotic-resistant phenotypes among study isolates

Antibiotics	No.Isolates (n=164)	Percentage
8 Antibiotics		
ERY, GEN, LVX, OFX, OXA, PEN, TOB, AMC	24	(n=1) 15%
7 antibiotics		
ERY, GEN, LVX, OFX, OXA, PEN, TOB	3	
ERY, GEN, LVX, PEN, VAN, TOB, AMC	1	
ERY, GEN, LVX, OFX, PEN, TOB, AMC	6	
ERY, LVX, OFX, OXA, PEN, TOB, AMC	11	
ERY, GEN, LVX, OFX, PEN, VAN, TOB	1	
ERY, GEN, LVX, OXA, PEN, TOB, AMC	1	
ERY, GEN, LVX, OFX, OXA, PEN, TOB	2	
ERY, GEN, OFX, OXA, PEN, TOB, AMC	1	
GEN, LVX, OFX, OXA, PEN, TOB, AMC	6	
ERY, GEN, LVX, OFX, OXA, PEN, AMC	1	(n=33) 20%
6 Antibiotics		
ERY, GEN, LVX, OFX, TOB, AMC	2	
ERY, GEN, LVX, OXA, PEN, TOB	2	
ERY, OFX, OXA, PEN, TOB, AMC	2	
ERY, LVX, OFX, PEN, TOB, AMC	4	
ERY, GEN, LVX, OFX, PEN, TOB	3	
ERY, GEN, OFX, PEN, VAN, TOB	1	
ERY, LVX, OXA, PEN, TOB, AMC	2	
GEN, LVX, OXA, PEN, TOB, AMC	1	
LVX, OFX, OXA, PEN, TOB, AMC	7	
ERY, LVX, OFX, OXA, PEN, TOB	1	
GEN, LVX, OFX, OXA, PEN, TOB	2	
ERY, GEN, LVX, OFX, PEN, VAN	1	(n=28) 17%
5 Antibiotics		
ERY, OXA, PEN, TOB, AMC	2	
GEN, LVX, OXA, PEN, TOB	1	
ERY, GEN, OFX, TOB, AMC	1	
GEN, OFX, VAN, TOB, AMC	1	
ERY, OFX, PEN, TOB, AMC	4	
ERY, LVX, OFX, PEN, TOB	10	
ERY, GEN, OFX, PEN, TOB	3	
ERY, LVX, OFX, TOB, AMC	2	
GEN, LVX, OFX, TOB, AMC	1	
ERY, GEN, LVX, OFX, TOB	1	
ERY, OFX, OXA, PEN, TOB	2	
LVX, OXA, PEN, TOB, AMC	2	
GEN, OFX, OXA, PEN, AMC	1	
GEN, LVX, OFX, PEN, TOB	1	
OFX, OXA, PEN, TOB, AMC	2	
LVX, OFX, OXA, PEN, TOB	2	(n=36)22%
4 Antibiotics		
GEN, OXA, TOB, AMC	2	
ERY, OFX, PEN, TOB	9	
GEN, OFX, PEN, TOB	1	
ERY, OXA, PEN, TOB	1	
OFX, PEN, TOB, AMC	1	
ERY, OFX, TOB, AMC	1	
LVX, OFX, PEN, TOB	2	
ERY, LVX, OFX, PEN	1	
ERY, OFX, OXA, PEN	1	
OFX, OXA, PEN, AMC	1	(n=20) 12%
3 Antibiotics		
LVX, TOB, AMC	2	
OFX, PEN, TOB	8	
LVX, PEN, TOB	1	
ERY, PEN, TOB	1	
OXA, PEN, TOB	1	
ERY, GEN, OFX	1	
ERY, OFX, PEN	2	
LVX, OFX, PEN	1	(n=17)10.35%
2 Antibiotics		
OXA, PEN	1	

OFX, PEN	1	
OFX, TOB	1	
PEN, TOB	3	(n=6) 3.65%
Total	**164**	**100%**

**Note: ERY, erythromycin; OFX, ofloxacin; AMC, amoxicillin + clavulanic acid; OXA, oxacillin; TOB, tobramycin; GEN, gentamicin; PEN, penicillin; LVX, levofloxacin; VAN, vancomycin.*

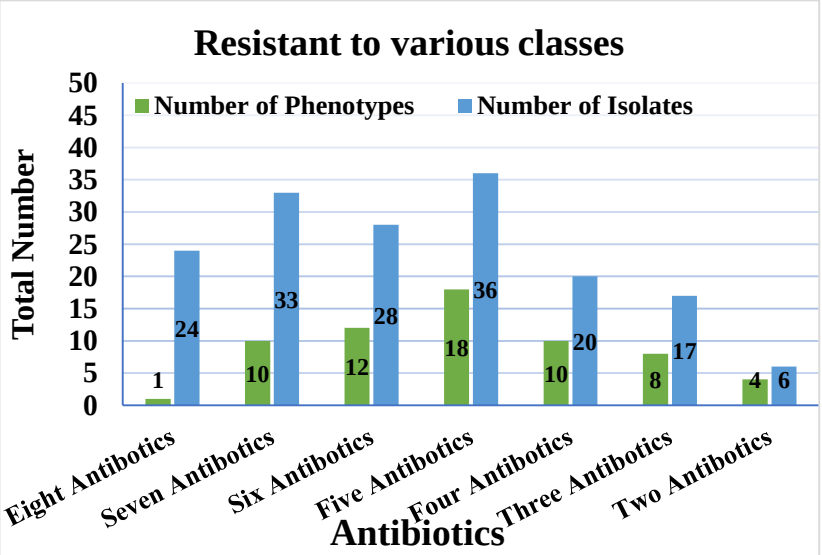

Figure 3: shows the overall statistics of resistance phenotypes i.e. The total number of isolates and the number of phenotypes.

A previous study from Pakistan reported that *Saprophyticus* was more prevalent in the age group ranging from 21-30 years (Bano et al., 2012), same findings were observed in the current investigation as most of the isolates were in the age group ranging from 21-30 years. The antibiotic resistance profile of *Saprophyticus* was noticed in a study from Kohat, Pakistan that all isolates were meropenem sensitive, while resistance against ciprofloxacin was 66.7%, followed by ceftazidime 100%, ceftriaxone 50%, cefepime 16% respectively (Ullah, Shah, Almugadam & Sadiqui, 2018).

In another study the resistance pattern of Gram-positive bacterial isolates having UTIs attending Khyber Teaching Hospital, Peshawar showed that *S. saprophyticus* was non-susceptible to amikacin (66.7%), followed by ampicillin (100%), amoxicillin (100%), augmentin (66.7%), azithromycin (88.9%), aztreonam (100%), cefotaxime (100%), ciprofloxacin (88.9%), ceftazidime (100%), gentamicin (55.6%), imipenem (33.3%), linezolid (77.8%), and ofloxacin (77.8%), respectively (Muhammad, Khan, Ali, Rehman & Ali, 2020). While in our study most of the isolates were resistant to

tobramycin (91%), ofloxacin (85%), and Penicillin (91%) respectively. These reports from the Peshawar region highlight the increased resistance pattern in these bacteria involved in UTI infections.

In the current investigation, the multi-drug resistance (MDR) pattern was observed in 96.3% of isolates, while a recent report from Pakistan reported a low prevalence of MDR in 1.7-18.64% of *S. saprophyticus* isolates (Hussain et al., 2021). The greater number of MDR in the present study may be due to the difference in the number of isolates, easy availability of antibiotics for public use, hospital management, host compatibility, and the non-availability of proper screening of antibiotic-resistant strains in the various geographical region of Pakistan. The resistance to the various classes of antibiotics in the current investigation will help the clinician in choosing the appropriate antibiotic for treating complicated UTIs.

Conclusion

The high prevalence of MDR in the case of *S. saprophyticus* poses a great challenge for healthcare providers. Resistance to various classes of antibiotics among *S. saprophyticus* poses a challenge soon for clinicians and public health experts which needs to be investigated.

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Conflict of interest

The authors have no conflict of interest.

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