Antibiotic Susceptibility Profiles of Coagulase-Negative Staphylococci Clinical Isolates Collected from Tertiary Care Hospital Peshawar

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Abstract

Coagulase-negative staphylococci (CoNS) are normal flora and significant colonizer in humans. Despite of these they become pathogenic during uncertain favorable conditions. It has been reported that colonizing CoNS pathogens are responsible for infections in humans, particularly in immunocompromised patients causing bacteremia as well as bloodstream infections. This study aimed to determine the antibiotic susceptibility profile of Coagulase-negative staphylococci clinical isolates collected from Tertiary Care Hospital Peshawar, Pakistan. A total of 120 clinical staphylococci isolates were collected from a Tertiary care hospital in Peshawar, Pakistan from January 2022 to April 2022. Samples were initially identified through Gram-staining and were further confirmed for growth characteristics by mannitol salt agar (OXOID CM0085). Various biochemical tests were performed for further identification of CoNS such as the catalase test, tube coagulase test, and DNase test. Antibiotic susceptibility profiles were determined through the disc diffusion method by following Clinical and Laboratory Standard Institutes (CLSI) guidelines; 2021.Chi-square test was used to find any significance of the data using SPSS software. Among 120 isolates, the major source of the isolate was pus (n=74, 61.66%), followed by urine (n=22, 18.33%), and blood (n=11, 9.16%). The majority of the isolates were from the emergency ward (n=46, 38.33%). More CoNS was observed in male (n=72, 60%) as compared to female (n=48, 40%) patients. The highest infection of CoNS was in the age group of 21-30 years.

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Staphylococci isolates were highly resistant to penicillin G (n=106, 88.33%), followed by erythromycin (n=72, 60%), amoxicillin (n=70, 58.33%), ciprofloxacin (n=70, 58.33%), and gentamycin (n=53, 44.16%) while highest susceptibility was observed to vancomycin (n=7, 5.83%). Overall 30% of CoNS were MDR. Seven isolates showed resistance to different 4 classes of antibiotics, followed by 17 isolates to three classes of antibiotics. The association between the gender and antibiotics was found statistically non-significant. CoNS are now involved in infection and also their increased resistance to different antibiotics may pose a great threat to clinicians. This matter should be noticed quickly. The emergence of MDR patterns in CoNS isolates involved in various infections.

Keywords: Staphylococci, CoNS, Antibiotic Resistance, MDR

Introduction

Coagulase-negative staphylococci are normal flora and normal inhabitants in the humans being. They become pathogenic only in certain situations. It has been reported that colonizing CoNS pathogens are responsible for infections in humans, particularly in immunocompromised hosts and neonates. The normal flora of human skin and mucus membrane include Coagulase Negative Staphylococci (CoNS**)** (Mushtaq and Naim, 2015). CoNS are normally found on human skin and are abundant colonizers of humans. Certain situations make them pathogenic.

The increase in opportunistic infections rate and infections due to medical devices caused by CoNS has increased the interest in CoNS (von Eiff *et al*., 2002). Colonizing CoNS pathogens are responsible for infections in humans and especially in neonates and immunocompromised hosts (May *et al*., 2014). CoNS show resistance to multiple drug classes (Qu *et al*., 2010). The spreading of antibiotic resistance in CoNS and the increasing use of medical devices over recent years have increased the rate of CoNS infections. One of the pathogenic potentials of CoNS is their capability to build biofilms on indwelling medical devices (Otto, 2004). CoNS are usually harmless commensal and are commonly isolated pathogens in clinical microbiology laboratories around the globe (John and Harvin, 2007).

The most common CONS species that are isolated clinically is *S. epidermidis*. CONS infection is the most common bloodstream infection that is treated in pediatric and neonatal intensive care units (Venkatesh *et al*., 2006). The clinical manifestations of CoNS infections differ from that of *S. aureus* infections. Bacteremia caused by CoNS can be rarely life-threatening when treated promptly and

adequately. However, in immunocompromised patients, frank sepsis syndrome and the fatal outcome may occur due to the involvement of *S. lugdunensis* which is a more virulent species (von Eiff *et al*., 2002).

The process of conjugation is the main mechanism of acquiring the resistance determinants whereas plasmids and mobile genetic elements act to transfer resistance determinants between the same species or diverse species (Lim and Webb, 2005). Horizontal gene transfer can also help in developing resistance through mobile genetic elements via plasmids, transposons, and a staphylococcal cassette chromosome. A study from Rawalpindi, Pakistan, reported a total of 350 isolates, out of which 148 were MRSA and 46 were MRCoNS. According to this study, the antibiotic resistance pattern of MRCoNS isolates for penicillin was (97.82%), erythromycin (78.26%), gentamicin (69.56%), and ciprofloxacin (63.04%). However, all MRCoNS isolates showed susceptibility to vancomycin. MDR rates in MRCoNS isolates were recorded as 32.60% (Perveen *et al*., 2013). Few reports are available regarding the CoNS prevalence and their antibiotic susceptibility.

Another study from the Department of Microbiology, Army Medical College, Rawalpindi, Pakistan conducted from June 2011 to May 2012 reported resistance pattern for penicillin was (100%), ciprofloxacin (77%), erythromycin (93.1%), gentamicin (68.3%). From Saudi Arabia and Bangladesh antibiotic resistance in CoNS were also reported as 100% isolates were penicillin resistant (Aqel *et al*., 2023), and 70% isolates were ciprofloxacin followed by 80% and 14% to erythromycin and gentamicin, respectively (Fazal *et al*., 2023). Vancomycin is the only drug to which all of the MRCoNS isolates showed sensitivity (Gilani *et al*., 2016). This study aimed to determine the antibiotic susceptibility profile of Coagulase-negative staphylococci clinical isolates collected from Tertiary Care Hospital Peshawar, Pakistan.

Materials and Methods

A total of 120 clinical staphylococci isolates were taken from a tertiary care hospital, Hayatabad Medical Complex (HMC) in Peshawar, Pakistan from January 2022 to April 2022. These isolates were collected from a microbiology laboratory collected from various clinical sources including blood, pus, tissue, tips of the drain, cerebrospinal fluid (CSF), urine, Ethylene diamine-tetra-acetic acid (EDTA) swab, tracheal secretions, sputum. The information with respect to patient age, ward,

gender, and clinical specimen was also taken from the hospital database. Samples were initially identified through Gram-staining and were further confirmed by mannitol salt agar (OXOID CM0085). Various biochemical tests were performed for further identification of CoNS such as the catalase test, tube coagulase test, and DNase test.

Antibiotic Susceptibility Test

Disk-diffusion method: Kirby-Bauer test (Bauer *et al*., 1966) was used for Antibiotic susceptibility test. The results interpretation was done by using the Clinical and Laboratory Standard Institute (CLSI) 2021guidlines. Mueller Hinton agar (MHA) (Oxoid, UK) plates were prepared according to the manufacturer's instructions. A panel of different antibiotics was tested including ciprofloxacin (5 µg), erythromycin (15 µg), penicillin G (10 units), gentamicin (10 µg) and amoxicillin (25 µg) (Oxoid, UK) against the study isolates.

Determination of multidrug-resistant (MDR) CoNS

Characterization MDR was done using previously published criteria where bacteria showing resistance to three or more antimicrobial classes were termed MDR (Cohen *et al*., 2008, Pillar *et al*., 2008).

Statistical Significance

The association of gender with various antibiotics was observed that is statistically significant or not, using SPSS software. A P-*value* > 0.05 was considered statistically significant. The study null hypothesis was to find out the association of all antibiotics with gender used in this study.

Results

A total of 120 clinical staphylococci isolates were taken in this study. A major source of the isolate was pus (n=74, 61.66%), followed by urine (n=22, 18.33%) and then blood (n=11, 9.16%) (Figure 1 (a)). According to Gender more CoNS were observed in male (n=72, 60%) as compared to female (n=48, 40%) patients (Figure 1 (b)). Most of the isolates were from the Emergency ward (n=46, 38.33%) followed by Medical ICU (n=14, 33.33%) and General Medicine (n=14, 11.6%) (Figure 1 (c)). It was observed that the highest infection was in the 21-30 years age group followed by 41-50 years (Figure 1 (d)). In this age

group, the maximum resistance was shown to penicillin G (88.88%), ciprofloxacin, and erythromycin (62.96%) each, followed by amoxicillin (59.25%) as shown in (Table 1).

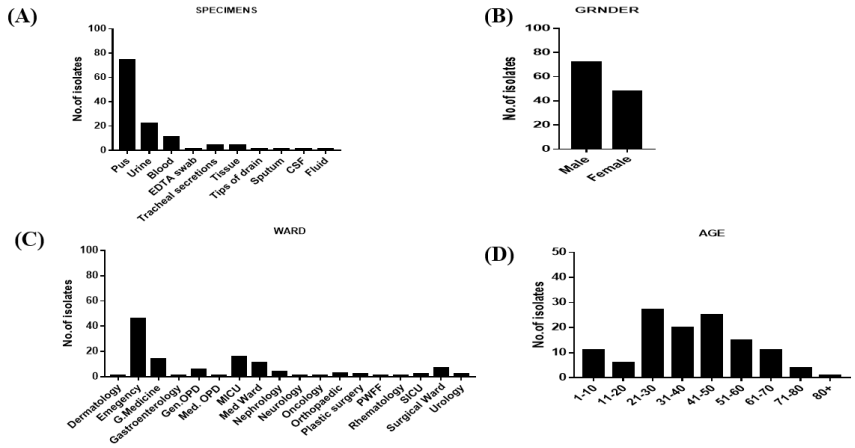


Figure 1: Demographic details of isolates. (A) Specimen wise distribution of isolates (B) Gender wise distribution of isolates (C) Ward wise distribution of isolates (D) Age wise distribution of isolates

Antibiotic susceptibility profile

Staphylococci isolates were highly resistant to penicillin G (n=106, 88.33%), followed by erythromycin (n=72, 60%), amoxicillin (n=70, 58.33%), ciprofloxacin (n=70, 58.33%), gentamycin (n=53, 44.16%) while lower resistance was shown to vancomycin (n=7, 5.83%) (Figure 2).

Prevalence of Multi-drug resistant (MDR) Isolates

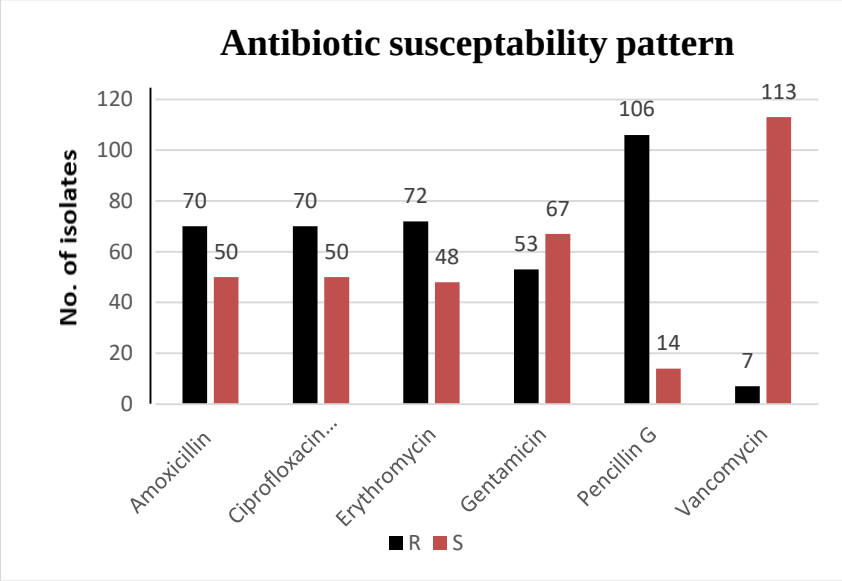
Overall 30% of CoNS were multi-drug resistant (MDR). According to our findings, 7 isolates showed resistance to 4 antibiotic classes, and 17 isolates were found resistant to three classes of antibiotics, while the rest of the details are shown in (Table 2).

Association of antibiotic resistance with gender

The association of gender with various antibiotics was observed as statistically non-significant in most of the data presented in Table 3. No association was found significant between these two variables (antibiotic and Gender) as shown in Table 3.

Table 1
Antibiotic resistance linkage with age group 21 to 30 years

Total isolates	***Amoxicillin***	***Ciprofloxacin***	***Erythromycin***	***Gentamicin***	***Penicillin G***	***Vancomycin***
27	59.25%	62.96%	62.96%	37.03%	88.88%	0%



`1**Figure 2: Shows the antibiotic susceptibility profile of CoNS isolates assessed by disk diffusion method against various antibiotics**

Discussion

In the current study, more CoNS were found in male (n=72, 60%) than female (n=48, 40%) patients. The same finding was observed in another study, which shows that CoNS in male patients (56.68%) is greater than in female samples isolated from various clinical specimens (Mehdinejad *et al*., 2008). Few studies are available regarding the prevalence and antibiotic resistance profile of CoNS from Pakistan. In another study of various clinical samples from Jaipur, India that out of a total of 60 isolates, 53.33% of isolates were taken from males while 46.67% were from female patients (Sangwan and Kumari 2018). As compared to these findings, another report from India showed that the majority of the CoNS isolates recovered from females (74.8%) as compared to males (25.2%) (Singh *et al*., 2022).

Table2

Resistance of CoNS against various classes of Antibiotics

Antibiotics	No. of Isolates	Percentage
No resistance	5	4.16%
One Antibiotic class		
P	38	31.66%
Two Antibiotic classes		
MP	14	11.66%
PF	17	14.16%
FM	2	1.667%
AG	1	0.83%
AP	6	5%
MA	1	0.83%
Three Antibiotic classes		
PMA	6	5%
PFM	3	2.5%
PFA	17	14.16%
PMG	1	0.83%
Four Antibiotic classes		
PFAG	1	0.83%
PFMA	7	5.83%
Five Antibiotic classes		
PFMAG	1	0.83%

P: Penicillin, F: Fluoroquinolones, M: Macrolide, A: Aminoglycoside, G: Glycopeptides

Table 3

Association of antibiotic resistance with gender

Variable	Erythromycin				*P*-value	Gentamicin				*P*-value	Amoxicillin				*P*-value
	R	I	S	Total		R	I	S	Total		R	I	S	Total	
Male	42	0	30	72		30	0	42	67		54	0	18	72	
Female	35	0	13	48	0.103	20	0	28	97		30	0	18	48	
Grand Total	77	0	43	120		50	0	70	120	1.00	84	0	36	120	0.143
Variable	**Penicillin-G**				***P*-value**	**Vancomycin**				***P*-value**	**Ciprofloxacin**				***P*-value**
	R	I	S	Total		R	I	S	Total		R	I	S	Total	
Male	70	0	2	72		6	0	66	48		46	0	26	72	
Female	45	0	3	48	0.351	3	0	45	72	0.671	23	0	25	48	0.083
Grand Total	115	0	5	120		9	0	111	120		69	0	51	120	

In the current study, a major source of the isolate was pus (n=74, 61.66%), followed by urine (n=22, 18.33%) and then blood (n=11, 9.16%). In another report from Manipur, India, the majority of CoNS isolates were collected from urine n=88 (65.2%), followed by blood n=37 (27.5%) and n=pus 3 (2.2%) (Singh *et al*., 2022). Another previous report from India the major source of the isolate was blood (34.7 %),

followed by urine (27.3%) and pus (9.3%) (Bhatt *et al*., 2016), while maximum CoNS isolates were collected from Urine samples (41.75%), followed by Pus (24%), Blood (4.25%) in India (Sangwan and Kumari 2018). A study of clinical isolates shows that out of a total of 120 samples, the strains isolated from blood were 68 followed by 52 strains from pus samples (Bora *et al*., 2018). The variation in the prevalence of CoNS from various sample sources may be due to the normal flora of the body, number of isolates, collection method, and maybe the site of infection from which the samples were taken.

In the present study, most of the isolates were from the emergency ward (n=46, 38.33%) followed by medical ICU (n=14, 33.33%) and general medicine (n=14, 11.6%). Another study from a tertiary care center shows that the majority of 73/150 isolates were from ICU (48.7%), and 18 were from acute wards (12%) (Bhatt *et al*., 2016). In the present study, it was observed that the highest infection (22.5%) was in the age group of 21-30 years. According to previous findings (29%) MRCONS were seen among patients with age 21-40 years (Mehdinejad *et al*., 2008). A similar finding was observed in another study from the tertiary care hospital of Manipur, India where the 20-29 years age group presented major CoNS isolates (28.88%) (Singh *et al*., 2022). A report from India shows the Maximum number of CoNS isolates in the age group 21-30 years **(**Bhatt *et al*., 2016). A report from Tertiary Care Teaching Hospital, Jaipur, India described that out of a total of 400 samples, the maximum isolates were in the range of 21-30 years i.e. 25 % (Sangwan and Kumari 2018).

In the current study, Staphylococci isolates were highly resistant to penicillin G (n=106, 88.33%), erythromycin (n=72, 60%), amoxicillin (n=70, 58.33%), ciprofloxacin (n=70, 58.33%), gentamicin (n=53, 44.16%) while lower resistance was shown to vancomycin (n=7, 5.83%). One study from Rawalpindi, Pakistan showed a drug resistance pattern for penicillin (97.82%), followed by erythromycin (78.26%), gentamicin (69.56%), ciprofloxacin (63.04%). A (100%) vancomycin sensitivity was recorded for all MRCoNS strains (Perveen *et al*., 2013). Another study from Punjab, Pakistan reported amoxicillin clavulanic acid sensitivity as (22.2%), ciprofloxacin (46.5%), erythromycin (11.9%), gentamicin (44.2%), and vancomycin (96.0%) (Sarwar *et al*., 2020). One study from Referral Center in South Italy reported resistance patterns for penicillin (86%), erythromycin (69%), amoxicillin-clavulanate (71%), ciprofloxacin (54%), and gentamicin (47%). All the strains showed no resistance to vancomycin (Nicolosi *et al*., 2020). The variation in

antibiotic resistance within the country may be due to the number of isolates, study duration, and geographical location. Another previous study from the tertiary care hospital of Manipur, India reported most isolates were resistant to penicillin (84.5%) followed by erythromycin (59.3%), and no resistance was seen to vancomycin (Singh *et al*., 2022).

One report of the Antibiotic susceptibility of CoNS isolates taken from very low birth weight babies showed most CoNS were resistant to penicillin G (100%), followed by gentamicin (83%). 100% susceptibility was recorded in ciprofloxacin and vancomycin (Qu *et al*., 2010). A study from Portugal recorded the highest rates of resistance for erythromycin (44%), followed by penicillin (38%), and gentamicin (25%). The lowest resistance was shown for ciprofloxacin (7%), and vancomycin (0%) (Oliveira and Cerca, 2013). In a previous report high resistance rate was recorded for erythromycin (91.7%) while a low resistance rate was observed for ciprofloxacin (37.5%), and gentamicin (25%) (Al-Tamimi *et al*., 2020). In the current study, 31.66% isolates showed resistant at the minimum to one class of antibiotics. Another study described that 69% of the isolates resistant at the minimum to one class of antibiotics from Portugal (Oliveira and Cerca, 2013). The variation in antibiotic resistance may be due to the number of isolates, study duration, geographical location, and the policy of antibiotic usage by hospitals.

In the current study, the prevalence of MDR was 30%. Another study reported close findings from Rawalpindi, Pakistan showed that 32.60% multidrug-resistant were identified as MRCoNS (Perveen *et al*., 2013). In another study from Germany, 23% (29/127) of MDR was reported (Marincola *et al*., 2021). One study from Portugal reported a 15% MDR value for CoNS isolates (Oliveira and Cerca, 2013). Other than MDR, the isolates also showed resistance to different class of antibiotics. Basically, the study null hypothesis was to find out the association of all antibiotics with gender used in the current study i.e. penicillin-G, fluoroquinolones (ciprofloxacin), erythromycin, gentamicin, amoxicillin, and vancomycin using SPSS, all our findings were non-significant (P-*value* >0.05). Variations in the MDR pattern in various reports could be due to the geographical location, sample selection, number of studies isolates, and the policy of antibiotic usage by hospital management. High prevalence of MDR in this study is alarming for clinicians as well as for other antibiotic resistance monitoring authorities which should be properly investigated.

Conclusion

In the case of staphylococci isolates 30% were characterized as MDR displayed a challenge for healthcare professionals that need to be investigated to overcome the problem. Most of the isolates showed resistance to various classes of antibiotics and limited therapeutic options for clinicians.

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Conflict of interest: Nothing to declare

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