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Win Lei Yee Mon
Associate Professor and Senior Consultant Microbiologist, Yangon General Hospital, Myanmar

Khin May OO
Professor & Head, Department of Public Health Laboratory, Yangon, Myanmar

MYA MYA AYE
Deputy Director, Bacteriology Research Division, Department of Medical Research, Yangon, Myanmar

NAN AYE Thida OO
Research Scientist, Bacteriology Research Division, Department of Medical Research, Yangon, Myanmar

CHO CHO OO
Professor & Head, Department of Microbiology, University of Medicine 1, Yangon, Myanmar

Correspondence
Win Lei Yee Mon
Associate Professor and Senior Consultant Microbiologist, Yangon General Hospital, Myanmar

Coagulase negative staphylococci from clinical isolates at tertiary care hospital, Myanmar

Win Lei Yee Mon, Khin May OO, MYA MYA AYE, NAN AYE Thida OO and CHO CHO OO

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Abstract
Coagulase negative staphylococci (CoNS) are a significant cause of hospital acquired infections and foreign body related infections. The antimicrobial resistance among CoNS is the increasing awareness in the hospital setting. Biofilm production is the major virulent factor of CoNS to give rise to infections. This study was conducted with the purpose of species identification, antimicrobial susceptibility, biofilm production and identification of *mecA* and *icaA* genes of CoNS isolated from clinical specimens. A total of 120 clinically significant CoNS were isolated from various clinical specimens in this study. The identification and antimicrobial susceptibility of CoNS was done by Vitek 2 compact system. Biofilm production was carried by Congo red agar plates test. The identification of *mecA* and *icaA* genes was detected by polymerase chain reaction. A total of 13 CoNS species were identified, *Staphylococcus haemolyticus* (33%), *Staphylococcus hominis* (32%) and *Staphylococcus epidermidis* (17%) were the most prevalent species. The methicillin resistance was 73% and *Staphylococcus haemolyticus* was the most resistant species to antimicrobials. Biofilm production was found as 43%. Eighty-six percent of CoNS were detected *mecA* gene and only 12% of them haboured *icaA* gene in this study. Studies on species diversity, antimicrobial resistance, and virulence of CoNS are of great importance because of their emerging role as pathogens. This study not only gave the information of antimicrobial resistant pattern and biofilm production but also the molecular determination of *mecA* and *icaA* genes among CoNS isolates for effective antimicrobial guideline policy and for future epidemiological studies.

Keywords: Coagulase negative staphylococci, antimicrobial resistance, biofilm production

1. Introduction
The clinical significance of coagulase negative staphylococci is increasing in hospital setting. Although they are contributing as normal flora in human body, they are also important pathogens in humans, causing a wide spectrum of life threatening diseases. The appearance of automated identification systems improved their detection and antimicrobial resistance [1].
Coagulase negative staphylococci (CoNS) are major group of staphylococci, containing 41 recognized species currently, many of which form part of the normal flora [2]. Within the last few years, CoNS have been increasingly recognized to cause clinically significant infections and are particularly associated with the use of medical devices. They are the most frequently isolated nosocomial pathogens, accounting for 34.1% of hospital associated infections [3]. Moreover they are becoming a problem in treating infections by showing a considerable amount of antibiotic resistance especially in hospital setting [4].
The antimicrobial resistance is highest in nosocomial infections because in hospitals, repeated contact with antibiotics leads to elimination of sensitive organisms from the flora and their substitution with resistant strains acquired by cross infection, especially CoNS. About 80%–90% of CoNS isolates associated with hospital infections are methicillin resistant coagulase negative staphylococci (MRCoNS). To a different extent, MRCoNS are additionally resistant to other classes of antibiotics [1].
Biofilm production is one of the most virulent factors of pathogenic CoNS. Nosocomial CoNS contribute more pathogenic manifestations because of their ability of biofilm production than that of the commensal CoNS. The initial bacterial monolayer adhering to polymeric surfaces is converted to a typical biofilm consisting of bacteria plus an extracellular slime substance. Adhesion, bacterial proliferation and slime production increase

antibiotic resistance, since drugs cannot be reachable to bacteria kept in slime layer. Molecular studies have shown that late phases of adherence, in which organisms first adhere to each other and then elaborate a biofilm, are mediated by polysaccharide intercellular adhesin (PIA), which is synthesized by products of the *ica* operon [5].

Eighty five percent of *Staphylococcus epidermidis* blood culture isolates contained the *ica* genes compared with 6% of commensal isolates, while a number of other studies have indicated that the *ica* locus may be a significant marker discriminating between significant and contaminating isolates [6].

The main challenge of CoNS is to differentiate the clinically significant pathogen from contaminants. The *mecA* and *icaA* genes are detected significantly more in infecting strains than in contaminating strains. Therefore, the identification of these two genes is necessary to confirm the isolate as infecting strain.

According to the emergence of nosocomial CoNS infection, this study was done to determine the antimicrobial susceptibility pattern, biofilm production and the two molecular determinants of CoNS for the purpose of increasing awareness about CoNS infections and hence studies on CoNS will facilitate in formulating and implementing particular antibiotic polices for treating CoNS infections and to control further emergence of drug resistant strains in future.

2. Materials and Methods

2.1. Bacterial isolates

Yangon General Hospital is 2000-beded tertiary hospital in Myanmar. It is the major public and teaching hospital, located in Yangon. In a laboratory-based cross-sectional study between March, 2020 and October, 2020, the clinical specimens sent for routine culture and susceptibility to Microbiology Laboratory, Clinical Pathology Department, Yangon General Hospital were included in the present study. A total of 120 CoNS isolates from various clinical specimens were investigated. The clinically significant CoNS isolates were collected according to the microbiological assessment of clinical relevance, and CoNS from mixed cultures were excluded. The isolates were stored in brain heart infusion broth with glycerol at -20 ℃.

2.2. Antimicrobial susceptibility

The species identification and antimicrobial susceptibility was determined by Vitek 2 compact system (biomereux, France). The antimicrobial susceptibility was determined by AST card (GP67) including benzylpencillin, oxacillin, gentamicin, ciprofloxacin, levofloxacin, moxifloxacin, erythromycin, clindamycin, quinupristin / dalfopristin, linezolid, vancomycin, tetracycline, tigecycline, nitrofurantoin, rifampicin and trimethoprim / sulfamethoxazole. *Staphylococcus aureus* ATCC 29213 was the control strain and the Vitek 2 minimum inhibitory concentration (MIC) results were interpreted using the Advanced Expert System of the Vitek 2.

2.3. Biofilm production

Biofilm production of CoNS isolates was evaluated by Congo red agar plate test in the present study. Congo red agar (CRA) was prepared by adding 0.8 g/L Congo red (Himedia), 50 g/L of sucrose and 10 g/L of agar powder (Oxoid) to 37 g/L of brain heart infusion broth (Himedia). Congo red stain was prepared as a concentrated aqueous solution and autoclaved separately from the other medium constituents, and was then added when the agar had cooled to 55 ℃. Plates were incubated for 24h at 37 ℃ and subsequently overnight at room temperature. Biofilm producing isolates grew as black colonies, while non-producing strains grew as red colonies.

2.4. Genotypic detection of *mecA* and *icaA* genes

The presence of *mecA* and *icaA* genes was analyzed by polymerase chain reaction using specific primers. The PCR primers for *mecA* gene were as follows: forward, 5′-AAAATCGATGGTAAAGGTTGGC-3′; reverse, 5′-AGTTCTGCAGTACCGGATTTGC-3′ [7]. The primer sequence for amplification of *icaA* gene was as follows: forward, 5′-TCTCTTGCAGGAGCAATCAA-3′; reverse, 5′-TCAGGCACTAACATCCAGCA-3′ [8]. DNA was extracted as follows: the bacterial growth was suspended in 150 µl of TE buffer. The bacterial suspension was boiled at 100 ℃ for 10 minutes in dry block heater and then the tube was placed on ice immediately for 5 minutes. After centrifugation at 10,000 g for 2 minutes, the supernatant containing crude genomic DNA was transferred into new tube and kept at -20 ℃. The reaction mixture was in a 20 µl volume containing the primers (0.25 µM each), together with 4 µl of the template DNA (approximately 50 ng/ µl), 250 µM of dNTPs, 0.5 U of Taq DNA polymerase, and 1xPCR buffer (20 mM Tris-HCl (pH-8.0), 100 mM KCl, 0.1 mM EDTA, 0.5% Tween 20, 1 mM DTT, 50% glycerol). The PCR reaction was programmed as follows: incubation at 95 ℃ for 5 min, followed by 35 cycles of 95 ℃ for 30 s (denaturation), 60 ℃ for 30 s (annealing), 72 ℃ for 1 min (extension), and final extension at 72 ℃ for 3 min [9]. After amplification, the PCR products were analyzed by 2% agarose gel electrophoresis for visualization.

3. Results

3.1. Distribution of CoNS in various clinical specimens

The various clinical specimens include blood, urine, sputum, wound swabs, pus, neck line, suction tip and catheter tip. They were categorized as follows: blood culture isolates, wound culture isolates, sputum culture isolates, urine culture isolates, and others including neck line, suction tip, and catheter tip. The coagulase negative staphylococci were isolated from blood (85/120, 71%), wound swab (17/120, 14%), urine (7/120, 6%), sputum (6/120, 5%) and others (5/120, 4%) respectively (n=120).

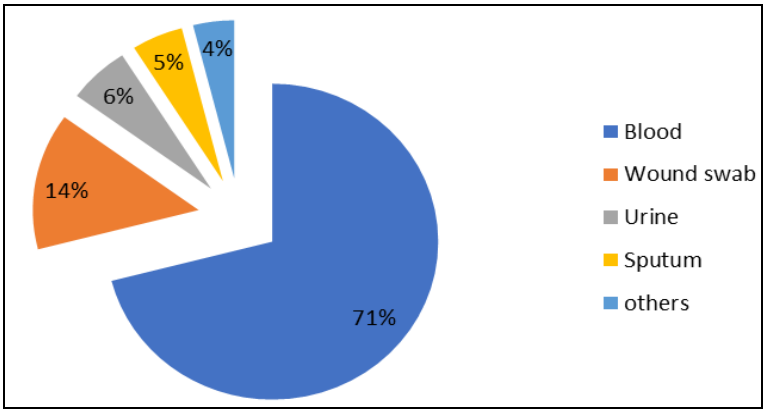


Fig 1: Distribution of CoNS in various clinical specimens

It was found that the majority of CoNS isolates were recovered from blood culture in the present study. According to the previous study in our setting, a total of 711 CoNS isolates were recovered throughout the year.

They were recovered from blood culture (416/711, 59%), wound culture (135/711, 19%), sputum culture (130/711, 18%) and urine culture (30/711, 4%) respectively. It has been noted that CoNS were mostly isolated from blood culture since the previous years. There might be the cause of high isolation rate of CoNS from blood culture; (1) the result came out from one blood culture set in most of the situations, (2) weakness in skin preparation before blood collection.

Determination of whether an isolate of CoNS represents true bacteremia was difficult. Several indicators have been investigated in order to differentiate true bacteremia from contamination, including number of positive blood cultures, species of CoNS, slime test result and antimicrobial susceptibility testing. The occurrence of more than one positive blood cultures has been used as a good predictor of true bacteremia. However, a combination of clinical or microbiological criteria was needed to judge a true bacteremia. The useful parameters for patients with only one blood culture positive for CoNS were incubation time until positive and slime production [10].

Among the CoNS infected patients, the youngest was 13 years and the oldest was 92 years while the mean age was 51.3 years. The most affected age group was 40-60 years, being 39%. Out of 120 infected patients, 73 (61%) were males and 47 (39%) were females. It was found that CoNS infection was more prevalent in males than females.

3.2. Species distribution of CoNS isolates

Among 120 CoNS isolates, 13 species of CoNS were detected in this study. The most common species were *Staphylococcus haemolyticus* (40/120, 33%), *Staphylococcus hominis* (38/120, 32%) and *Staphylococcus epidermidis* (20/120, 17%). *Staphylococcus saprophyticus* (5/120, 4%), *Staphylococcus warneri* (4/120, 3%), *Staphylococcus cohnii* (3/120, 2%), *Staphylococcus sciuri* (3/120, 2%) and *Staphylococcus lugdunensis* (2/120, 2%) were found and the remaining *Staphylococcus capitis*, *Staphylococcus lentus*, *Staphylococcus pseudointermedius*, *Staphylococcus simulans* and *Staphylococcus xylosus*, being (1/120, 1%) each. These findings were in agreement with the other studies [11-14].

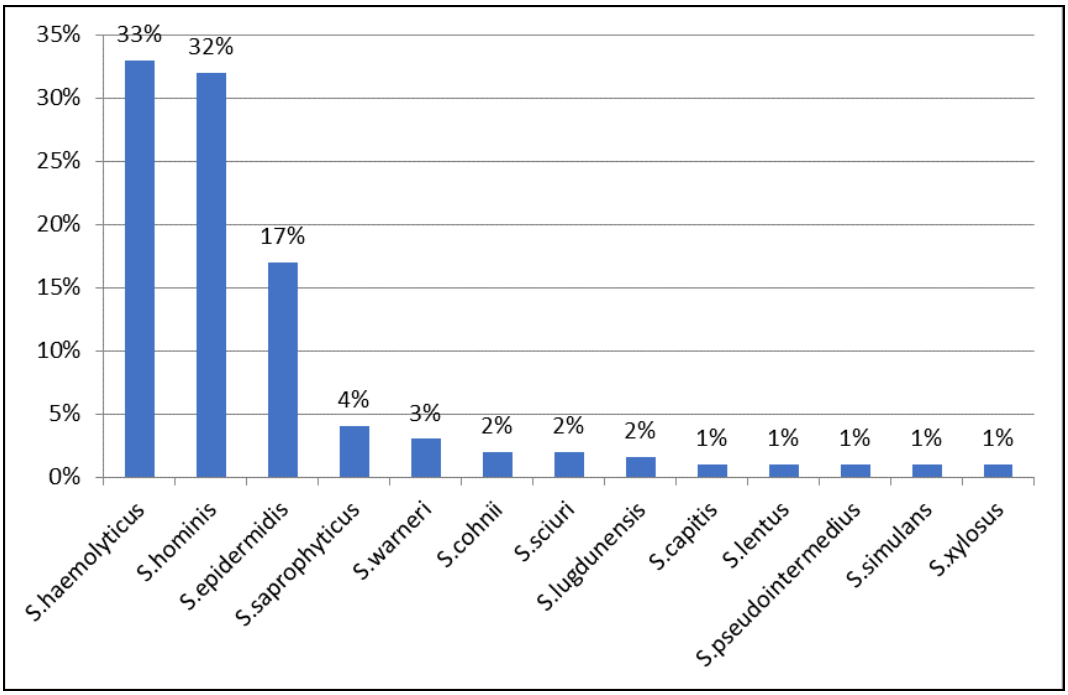


Fig 2: Species distribution of CoNS isolates

The slight variation in species isolated may be due to the variation of specimen collection methods, variation of patients' conditions, different methods for species identification and the species predominating in various geographical areas. It was observed that *Staphylococcus haemolyticus* was the predominant species of CoNS in our setting during these years. Particular species of CoNS are associated with distinct types of infections and patterns of antimicrobial susceptibility. Because of increasing clinical significance of CoNS, accurate species identification of CoNS is highly desirable to permit a more precise determination of host-pathogen relationship of CoNS [15].

3.3. Antimicrobial susceptibility of CoNS

The antimicrobial susceptibility pattern of CoNS showed that they were mostly resistant to penicillin (91%), oxacillin (77%), erythromycin (72%), clindamycin and cotrimoxazole (45%) each, rifampicin (40%), ciprofloxacin (31%), tetracycline (27%), moxifloxacin (23%), levofloxacin, gentamicin, quinupristin/dalfopristin, vancomycin, and tigecycline (14%) each, linezolid and nitrofurantoin (9%) respectively.

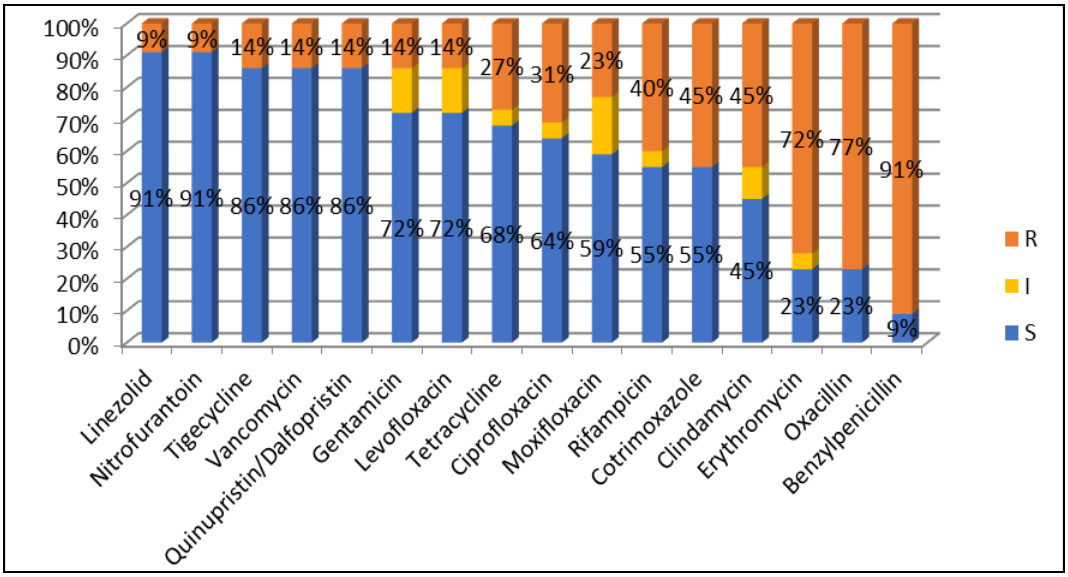


Fig 3: Antimicrobial susceptibility of CoNS

Resistance to penicillin, erythromycin and quinolone was detected in almost all species and all types of clinical specimens, and therefore, these three antibiotics could not be recommended as empirical therapy for CoNS infections. The resistance to cotrimoxazole, aminoglycoside, tetracycline and rifampicin was slightly lower in some species, but still very high, and these antibiotics mush be cautiously selected. Not surprisingly, consistent with most previous studies, the efficacy of vancomycin, linezolid, tigecycline, nitrofurantoin and quinupristin/dalfopristin was still good against CoNS infections.

3.4. Methicillin resistant coagulase negative staphylococci: Among 120 CoNS isolates, it was found that 73% (87/120) were methicillin resistant and 27% (33/120) were methicillin susceptible. Among the methicillin resistant CoNS (MRCoNS), methicillin resistant gene (*mecA*) was detected in 86% (75/87) while the remaining 14% (12/87) were not detected *mecA* gene. These methicillin resistant CoNS were mainly isolated from the medical units (44%), followed by surgical units (13%). The isolation rate from intensive care unit was low (2%) in the present study.

According to the previous studies [16-19], the methicillin resistance of CoNS was significantly higher around the world, ranging from 70-90% in the hospital settings. This was an important issue in antimicrobial resistance era.

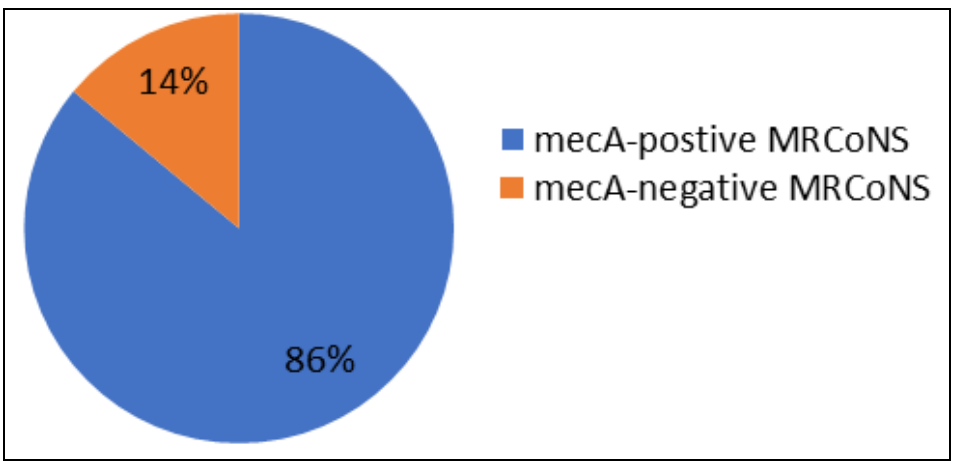
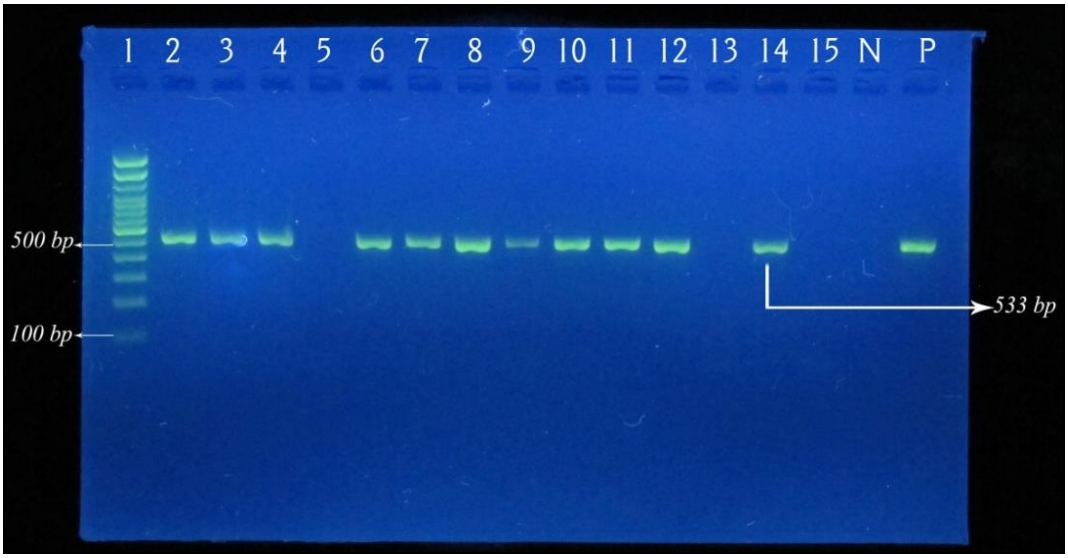


Fig 4: Proportion of *mecA* gene in CoNS isolates



Lane 1= 100 bp DNA marker; Lane 2-15 = PCR products; N = negative control; P = Positive control.

Fig 5: Agarose gel electrophoresis of *mecA* gene

The *mecA* gene was found in (36/39, 92%) of *Staphylococcus haemolyticus*, (20/25, 80%) of *Staphylococcus hominis*, (9/10, 90%) of *Staphylococcus epidermidis*, (1/3, 33%) of *Staphylococcus saprophyticus*, (1/2, 50%) of *Staphylococcus sciuri* and all isolates of *Staphylococcus cohnii*, *Staphylococcus warneri*, *Staphylococcus lentus*, *Staphylococcus lugdunensis*, *Staphylococcus pseudointermedius* and *Staphylococcus simulans*.

The high prevalence of methicillin resistance not only decreases the treatment options and also assists in transfer of resistant genes to other staphylococcal strains present in the hospital settings. The long hospital stay, frequent invasive medical procedures, use of multiple antimicrobials and chronic debilitated patients could be the risk of high occurrence of methicillin resistance. The increasing morbidity and mortality due to infections was because of the increased resistance rate to antimicrobials.

The presence of *mecA* gene in CoNS points out the existence of resistant elements and has the potential to transfer resistance mechanisms to other virulent pathogens such as *Staphylococcus aureus* present on the skin and environment. Methicillin resistance in isolates that lack the *mecA* gene may be mediated by other mechanisms of methicillin resistance, such as possession of *mecC*, *mecB* genes, or the overproduction of β-lactamases.

The multidrug resistant CoNS are resistant to any 3 or more groups of antibiotics at the same time. In the present study, methicillin resistant CoNS are also found as multidrug resistant (p<0.01).

This finding was one of the critical issues in treating the patients with CoNS infections. It pointed out the important role of antimicrobial resistance pattern and it should be followed according to the antimicrobial guidelines.

Table 1: Methicillin resistant vs multidrug resistant

	Multidrug resistant				Total	
	+	%	-	%		
Methicillin resistant	70	80.46	17	19.54	87	100
Methicillin susceptible	2	6.06	31	93.94	33	100
Total	72	60	48	40	120	100

Fisher exact value <0.001

3.5. Slime producing coagulase negative staphylococci

Previous reports have suggested that slime has a role in the pathogenesis of CoNS infections. Both slime production and the species of the organism appeared to be crucial factors in the determination of pathogenicity [1].Out of 120 CoNS isolates, the slime producing CoNS were found to be 43% (52/120) and the rest 57% (68/120) were non slime producers.

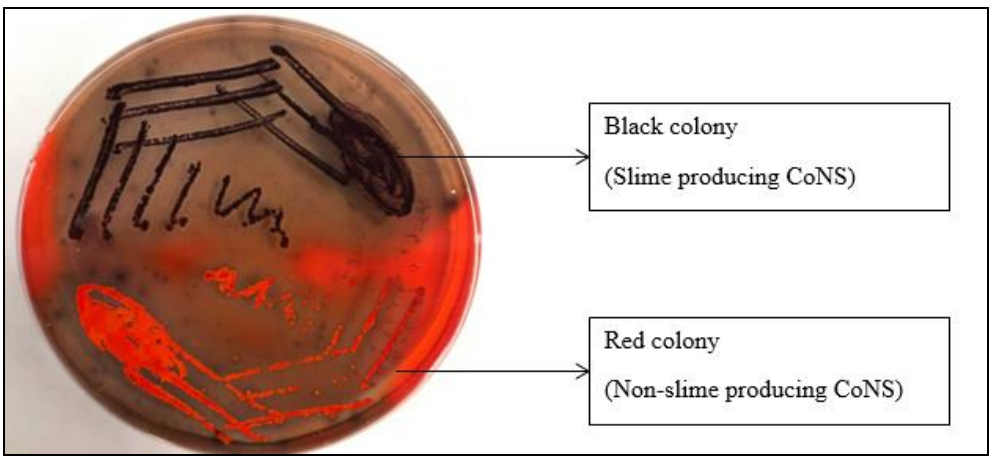
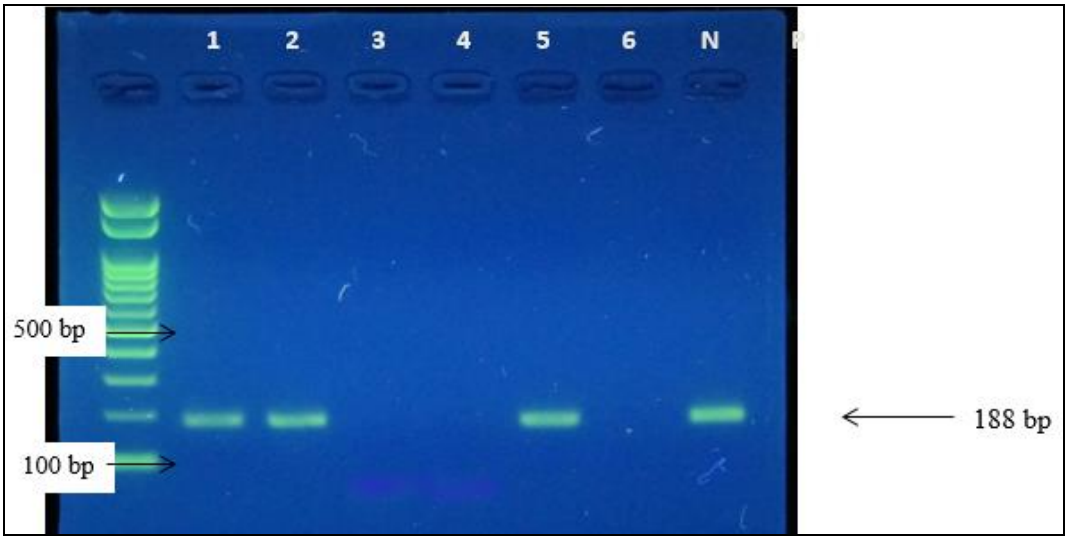


Fig 6: Congo red agar

Among 52 slime producing CoNS isolates, *Staphylococcus hominis* was the predominant species, being (23/52, 44%), which was followed by *Staphylococcus* haemolyticus (14/52, 27%), *Staphylococcus epidermidis* (12/52, 23%) and (1/52, 2%) each of *Staphylococcus warneri*, *Staphylococcus lugdunensis* and *Staphylococcus simulans* (n=52). The slime producing CoNS isolates were recovered from wound specimens (53%), followed by urine (43%), other specimens (40%), blood (42%) and sputum (33%).

The virulent gene *icaA* was detected in 12% (6/52) while the remaining 88% (46/52) were *icaA*-negative (n=52).



Lane 1 = 100 bp DNA marker; Lane 2-6 = PCR products; N = negative control; P = positive control.

Fig 7: Agarose gel electrophoresis of *icaA* gene

There was 33% (4/12) of *Staphylococcus epidermidis*, 7% (1/14) of *Staphylococcus haemolyticus* and 4% (1/23) of *Staphylococcus hominis* found as *icaA*-positive slime producing CoNS isolates in this study. It was not detected in *Staphylococcus warneri, Staphylococcus lugdunensis* and *Staphylococcus simulans.*

This study may be limited by the lack of comprehensive clinical data of the patients as well as the lack of evaluation of *icaD, icaB* and *icaC* genes. However, the information of clinically significant CoNS was obtained from this study and it was noticed that CoNS as pathogens in hospital setting. It would also be helpful for providing antimicrobial guideline policy and for further epidemiological studies.

4. Conclusion

Studies on species diversity, antimicrobial resistance, and virulence factor of CoNS are of great significance because of their emerging role as pathogens. As the distribution of various CoNS species in human population can vary, species identification from various clinical specimens is very important. In this study, based on the phenotypic identification, 13 species of CoNS were detected and *Staphylococcus haemolyticus* was found to be the major species isolated.

The antimicrobial resistance of CoNS showed high resistance to penicillin, erythromycin, quinolone and cotrimoxazole. The most susceptible antibiotics were linezolid, nitrofurantoin, quinupristin / dalfopristin, tigecycline and vancomycin. *Staphylococcus haemolyticus* was the most resistant species to antibiotics.

There was 73% methicillin resistance in isolated coagulase negative staphylococci. Ninety-eight percent of *Staphylococcus haemolyticus*, 66% of *Staphylococcus hominis* and 50% of *Staphylococcus epidermidis* were found to be methicillin resistant. The methicillin resistance was not found in *Staphylococcus capitis* and *Staphylococcus xylosus.*

The *mecA* gene was detected in 86% of methicillin resistant CoNS. It was detected in 92% of *Staphylococcus haemolyticus*, 90% of *Staphylococcus epidermidis* and 80% of *Staphylococcus hominis*. Moreover, the most important and life threatening factor was most of the methicillin resistant CoNS were found to be multidrug resistant to antimicrobials. This impact must be considered as major issue in providing antimicrobial guideline policy.

The slime producing was found as 43% of isolated CoNS. The predominant species of slime production was *Staphylococcus hominis* (44%), followed by *Staphylococcus haemolyticus* (27%) and *Staphylococcus epidermidis* (23%). The slime producing CoNS isolates were mostly recovered from wound specimens.

The *icaA* gene was detected in 12% of slime producing CoNS isolates. The gene detection was highest in *Staphylococcus epidermidis* (33%), 7% of *Staphylococcus haemolyticus* and 4% of *Staphylococcus hominis.*

The detection of antimicrobial resistance and slime production of CoNS showed their clinical importance. The high carriage of *mecA* gene was indicative of CoNS as reservoir of resistant genes in the hospital environment. Therefore, the antibiotics should be used according to antimicrobial guidelines to prevent the further spread of resistance.

This study was the first report of the clinically significant CoNS in the hospital setting in our country. It provided the useful information for the antimicrobial guideline policy and highlighted the needs for further epidemiological studies.

5. Acknowledgement

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Conflict of Interest

Not available

Financial Support
Not available

7. References

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