Original article

Determination of antimicrobial resistance profile and inducible clindamycin resistance of *coagulase negative staphylococci* in pediatric patients: the first report from Iran

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Background: **Currently, *coagulase negative staphylococci* (CoNS) have got much attention as a serious health problem especially in neonates and children. High incidence of antibiotic resistance, in particular methicillin resistance, has complicated the treatment of these organisms. The aim of this study is to determine the susceptibility to different antimicrobial agents and the prevalence of macrolides-lincosamides-streptogramins B (MLS_B) resistance in CoNS isolates obtained from pediatric patients.**

Methods: **Totally 157 CoNS isolates from various clinical samples were examined for antibiotic resistance using disk diffusion and E-test methods. Double-disk test was applied to detect constitutive and inducible MLS_B resistance ($cMLS_B$ and $iMLS_B$) phenotypes.**

Results: **Resistance to methicillin was seen in 98 (62.4%) isolates. All isolates were susceptible to vancomycin and linezolid. The prevalence of resistance to antibiotics tested was as follows: fusidic acid (*n*=58, 36.9%), gentamicin (*n*=73, 46.5%), ciprofloxacin (*n*=81, 51.6%), clindamycin (*n*=112, 71.3%), erythromycin (*n*=129, 82.2%) and trimethoprim/sulfamethoxazole (*n*=133, 84.7%). $iMLS_B$ phenotype was seen in 14 (8.9%) isolates, and 18 (11.5%) and 98 (62.4%) isolates showed MS and $cMLS_B$ phenotypes, respectively. We observed that high overall antibiotic resistance rates were associated significantly with methicillin resistance. Conversely, $iMLS_B$ phenotype was correlated neither with methicillin resistance nor with invasiveness.**

Conclusion: **Given the similarity observed between the prevalence of $iMLS_B$ and MS phenotypes, the performance of disk diffusion induction test is strongly recommended in our region.**

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Key words: **antibiotic susceptibility;**
***coagulase negative staphylococci*;**
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Introduction

Pediatrics and neonates are one of the most vulnerable groups to be infected with *coagulase negative staphylococci* (CoNS).[1-3] However, these infections are frequently ignored, particularly in our region, because most of the clinicians consider CoNS strains as contamination. On the other hand, the exotic power of CoNS to adapt to antibiotic pressure as well as their ability to act as a source of resistance determinants, impose a serious burden on the public health systems.[4,5] The Macrolides-Lincosamides-Streptogramins B (the so-called MLS_B) is a group of antibiotics commonly used in the treatment of staphylococcal infections, but unrestricted consumption has increased the rate of resistance to these drugs.[6] In this field, two main mechanisms are involved: 1) active efflux mechanism encoded by *msrA*, affecting macrolides and type B streptogramins, which results in MS phenotype (resistance to macrolides and group B streptogramins and susceptibility to lincosamides); and 2) target site modification via 23S rRNA methylation encoded by *erm* genes which confers constitutive or inducible resistance to MLS_B agents.[7] Strains with constitutive MLS_B resistance ($cMLS_B$) phenotype show resistance to all MLS_B drugs without any need to an inducer. In contrast, in inducible MLS_B resistance ($iMLS_B$), exposure to a strong methylation inducer

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(e.g., erythromycin) results in the expression of resistance to lincosamides and streptogramins B.[7] However, it has been demonstrated that spontaneous mutations can transform $iMLS_B$ phenotype to $cMLS_B$, without the presence of an inducer.[8]

In clinical practice, relying just on the standard broth-based or agar dilution methods leads to misidentification of $iMLS_B$ phenotype and consequently failure treatment as a result of clindamycin therapy. On the other hand, considering all erythromycin-resistant strains as clindamycin resistant, makes the effect of latter drug underestimate in infections caused by clindamycin-susceptible isolates. Hence, using an appropriate method like double disk diffusion method in order to determine MLS_B phenotypes would be very informative to better control of CoNS infections.

In the present study, we aimed to determine the susceptibility pattern of CoNS strains in pediatric patients aged between 0-10 years old. Moreover, determination of MLS_B resistance including $iMLS_B$ phenotype was investigated.

Methods

From February 2012 to October 2013, a total of 157 consecutive, non-duplicated clinical isolates of CoNS, were collected from microbiology laboratories of two largest university affiliated hospitals: Pediatric Hospital of Tabriz (Tabriz, Iran) and Iranian Referral Children's Hospital (Tehran, Iran). Simultaneously, clinical signs and some laboratory data related to each patient were recorded. In neonates, their clinical significance was determined according to the criteria proposed by Stoll et al.[9] Briefly, CoNS bloodstream infections in monobacterial positive blood cultures combined with C-reactive protein >10 mg/L within two days of blood culture were considered as true infections. CoNS strains isolated from internal fluids or foreign bodies in pure primary cultures were classified as true infection. Other isolates were classified according to the Center for Disease Control and Prevention criteria for definition of nosocomial infections.[10]

Amplification of the *tuf* gene was performed for all isolates in order to identify *Staphylococcus epidermidis* isolates.[11] Isolates that were not recognized as *S. epidermidis* were identified to the species level, using Microgen Staph ID kit (Microgen Bioproducts, UK), according to the manufacturer's instruction.

Methicillin resistance was detected phenotypically by disk diffusion method using cefoxitin (30 μg) and oxacillin (1 μg) disks (MAST, UK) and confirmed by amplification of the *mecA* gene.[12] Antibiotic susceptibility pattern was determined by disk diffusion method, according to the Clinical and Laboratory Standards Institute guideline.[13] The antibiotics tested included: gentamicin (10 μg), erythromycin (15 μg), clindamycin (2 μg), ciprofloxacin (5 μg), fusidic acid (10 μg), trimethoprim/sulfamethoxazole (1.25/23.75 μg) and linezolid (30 μg) (Mast, UK). The minimum inhibitory concentration of vancomycin was determined by E-test (Liofilchem, Italy). Results were also interpreted according to the CLSI breakpoints.[13] Isolates showing intermediate/resistance to erythromycin and intermediate/susceptibility to clindamycin were further analyzed for $iMLS_B$ phenotype using D-test. For this purpose, erythromycin and clindamycin disks were placed 20 mm apart from center to center onto inoculated Mueller-Hinton agar plates. After 18 hours of incubation at 35°C, flattening of inhibition zone (D- shaped zone) around clindamycin was considered as positive D-test ($iMLS_B$ phenotype). Isolates showing resistance to clindamycin were classified as $cMLS_B$ phenotype and circular inhibition zone around clindamycin was attributed to MS pattern. Statistical analysis was performed using chi-square test by IBM SPSS Statistics version 21. $P<0.05$ was considered statistically significant.

Results

From different clinical samples, including blood 109 (69.4%), tracheal tube 13 (8.3%), catheter 12 (7.6%), wound 8 (5.1%), eye 4 (2.5%), cerebral shunt 3 (1.9%), urine 3 (1.9%), ear secretion 2 (1.3%), ascetic fluid 2 (1.3%) and cerebral spinal fluid 1(0.6%), we found *S. epidermidis* to be the most prevalent species (n=97), followed by *Staphylococcus hominis* (n=16), *Staphylococcus schleiferi* (n=9), *Staphylococcus caprae* (n=6), each of *Staphylococcus haemolyticus* and *Staphylococcus capitis* (n=5), each of *Staphylococcus warneri*, *Staphylococcus hyicus* and *Staphylococcus cohnii* (n=4), *Staphylococcus auricularis* (n=3), *Staphylococcus lugdunensis* (n=2), and each of *Staphylococcus chromogenes* and *Staphylococcus intermedius* (n=1).

Methicillin resistance was detected in 98 (62.4%) isolates. Invasive strains were significantly more resistant to methicillin in comparison with contaminants ($P<0.05$). Similar association was also found in methicillin resistance between *S. epidermidis* and other CoNS isolates. All isolates were susceptible to vancomycin and linezolid. The prevalence of resistance to other antimicrobial agents was as follows: fusidic acid (n=58, 36.9%), gentamicin (n=73, 46.5%), ciprofloxacin (n=81, 51.6%), clindamycin (n=112, 71.3%), erythromycin (n=129, 82.2%) and trimethoprim/sulfamethoxazole (n=133, 84.7%).

The antibiotic susceptibility patterns of methicillin-resistant (MR) and methicillin-susceptible (MS) CoNS in invasive and contaminant groups are shown in Table 1.

Methicillin resistance had significant association (P<0.001) with resistance to gentamicin [Spearman's correlation coefficient (SCC)=0.43], erythromycin (SCC=0.36), clindamycin (SCC=0.28), ciprofloxacin (SCC=0.43), and fusidic acid (SCC=0.32). The associations between invasiveness and resistance to gentamicin (P=0.001), clindamycin (P=0.03), ciprofloxacin (P=0.007) and fusidic acid (P=0.003), were also significant. Table 2 shows the prevalence of $cMLS_B$, $iMLS_B$ and MS phenotypes in MR- and MS-CoNS isolates. Among isolates appearing D-test positive, 12 (85.7%) isolates were identified as *S. epidermidis* and the other two remaining ones were *S. hominis* and *S. auricularis*. Comparing MR- and MS-CoNS isolates, $cMLS_B$ phenotype was statistically more positive among MR-CoNS [odds ratio (OR)=3.4; 95% confidence interval (CI)=1.7-6.8; P<0.001]. However, there was neither correlation between $iMLS_B$ phenotype and methicillin resistance (OR=0.57; 95% CI=0.19-1.7; P=0.38) nor between invasiveness and $iMLS_B$ pattern (P=0.78). Analysis of multidrug resistant (MDR) isolates, i.e. showing resistance to at least three antibacterial agents, revealed that 85% of isolates were classified as MDR. Additionally, 27 (17.2%) isolates indicated resistance to all antibiotics tested which contained 74% of invasive strains.

Discussion

CoNS strains, common colonizers of skin and mucous membranes, are frequently reported as nosocomial infections especially from neonates and children. Currently, the high incidence of antibiotic resistance, in particular methicillin resistance, has complicated the treatment of these organisms.[14]

The rate of methicillin resistance observed in our study (71.4% in invasive isolates and 55.1% in contaminants) was lower than that reported by Mert et al.[15] in which 91.1% of CoNS causing true bacteremia and 80.2% of contaminants were methicillin resistant. The prevalence of MR-CoNS in clinical samples has been reported between 55%-77% and even 86% in intensive care units, from different countries.[14] The high overall prevalence in methicillin resistance is a serious threat, as the most MR-CoNS strains show resistance to many widely used antibiotics.[16] Otherwise, transfer of *mecA*, the methicillin resistance-encoding gene, between CoNS species and *Staphylococcus aureus*, even in an individual patient develops more concerns.[17]

Totally, in this study, resistance rates of CoNS isolates to the antibacterial agents were considerably higher than those reported by two other studies in our country.[18,19] However, the incidence rate of resistance to gentamicin was similar to the study of Mamishi et al.[18] An investigation performed on 180 CoNS strains in Norway,[20] indicated that 76.5% of invasive strains and 56.8% of contaminants were resistant to gentamicin, which are relatively higher than those in our study (60.6% and 34.9%, respectively).

Table 1. Antibiotic susceptibility patterns of MR-CoNS and MS-CoNS isolates

Antibiotics	MR-CoNS (n=98)							MS-CoNS (n=59)						
	Invasive (n=50)			Contaminant (n=48)			Total resistance	Invasive (n=21)			Contaminant (n=38)			Total resistance
	S	I	R	S	I	R	n (%)	S	I	R	S	I	R	n (%)
Gentamicin	14	0	36	22	0	26	62 (63.3)	12	2	7	32	2	4	11 (18.6)
Erythromycin	1	1	48	4	1	43	91 (92.8)	6	0	15	14	1	23	38 (64.4)
Clindamycin	5	0	45	13	1	34	79 (80.6)	9	0	12	17	0	21	33 (55.9)
Fusidic acid	19	0	31	30	1	17	48 (49.0)	16	0	5	33	0	5	10 (16.9)
Ciprofloxacin	9	1	40	20	1	27	67 (68.4)	15	1	5	28	1	9	14 (23.7)
Trimethoprim/Sulfamethoxazole	7	0	43	4	0	44	87 (88.8)	3	0	18	10	0	28	46 (78.0)
Linezolid	50	0	0	48	0	0	0 (0.0)	21	0	0	38	0	0	0 (0.0)
Vancomycin	50	0	0	48	0	0	0 (0.0)	21	0	0	38	0	0	0 (0.0)

MR-CoNS: methicillin-resistant *coagulase negative staphylococci*; MS-CoNS: methicillin-susceptible *coagulase negative staphylococci*; S: susceptible; I: intermediate; R: resistant.

Table 2. MLS_B resistance phenotypes in CoNS isolates

Phenotypes	MR-CoNS			MS-CoNS			Total resistance n (%)
	Invasive (n=50)	Contaminant (n=48)	Total resistance n (%)	Invasive (n=21)	Contaminant (n=38)	Total resistance n (%)	
MS	4	9	13 (13.3)	3	2	5 (8.5)	18 (11.5)
$cMLS_B$	42	30	72 (73.5)	9	17	26 (44.0)	98 (62.4)
$iMLS_B$	3	4	7 (7.1)	3	4	7 (11.9)	14 (8.9)

MLS_B: macrolides-lincosamides-streptogramins B; CoNS: *coagulase negative staphylococci*; MS: erythromycin resistance, clindamycin susceptible; $cMLS_B$: constitutive MLS_B resistance (D-); $iMLS_B$: inducible MLS_B resistance (D+).

Approximately, 85% of our isolates were resistant to trimethoprim/sulfamethoxazole, and this is higher than that of reports from Iran (67%),[18] Turkey (53%)[16] and European countries (59%-62%), respectively.[14] Also, comparing invasive and contaminant groups in our study to the corresponding groups in a previous study from Turkey,[15] revealed that our isolates were more resistant to trimethoprim/sulfamethoxazole (85.9% and 83.7% *vs.* 58% and 56.1%, respectively). This antibiotic has been considered as an alternative drug in the treatment of methicillin-resistant staphylococci,[16] but our finding suggests that it is not a suitable agent in this region.

In the present study, fusidic acid as a second-line agent in the treatment of staphylococcal infections showed a resistance rate of 36.9% (50.7% in invasive strains and 25.6% in contaminants), which is significantly higher than that of reports (7.2%-20%) from North American and Australian hospitals.[21] In Turkey,[22] 40% of MR-CoNS isolates were resistant to fusidic acid which is similar to ours (49%). Although this antibiotic showed the lowest resistance in comparison with the other antibacterial agents, more careful surveillance strategies are necessary to avoid further resistance. This will be more highlighted due to the fact that *S. aureus* strains are reportedly more susceptible to fusidic acid in comparison with CoNS.[22]

In this study, no resistance to vancomycin and/or linezolid was seen. However, as decreased susceptibility to glycopeptides has been reported from some countries,[16] the use of these drugs as the last resorts in the treatment of staphylococcal infections may be limited in a few years, if medical practitioners are not concerned about the extensive use of these agents in the hospitals.

High frequency of MDR isolates, limitation for vancomycin therapy and changing patterns in antimicrobial susceptibility make clinicians reconsider medicines such as clindamycin. This antibiotic is mentioned as a good option for the treatment of both MR- and MS-staphylococcal infections in children and penicillin-allergic patients. Low gastrointestinal side effects, low cost, excellent tissue penetration, good accumulation in abscesses without renal dosing adjustment requirement are some of the advantages of clindamycin.[6,7] However, there is much reluctance on its prescribing because of concerns about treatment failure as a result of commonly reported inducible resistance. Fielbelkorn et al[7] demonstrated that the sensitivity of disk induction test for detection of $iMLS_B$ phenotype in CoNS strains was 100% at 20 mm and 26 mm. Here, we placed the related disks at 20 mm and found that 8.9% of our isolates showed $iMLS_B$ phenotype.

Different studies[23,24] have shown that the occurrence of $iMLS_B$ varies by geographic region, hospital, patient age and bacterial susceptibility pattern. To our knowledge, this is the first report about the prevalence of $iMLS_B$ phenotype in CoNS from Iran. Here, we found that the prevalence (8.9%) of $iMLS_B$ in our isolates was lower than 14.7% in Turkey,[6] but higher than 2.5% in Brazil.[25] In a study conducted in United States,[7] $cMLS_B$ phenotype was found in 70% of erythromycin resistant isolates, which is in agreement with ours (75%). But $iMLS_B$ phenotype was found in 30% of isolates, which is considerably higher than our finding. In another report from Turkey,[15] 33.1% and 31.3% of invasive and contaminant isolates showed $iMLS_B$ phenotype, which are higher than 8.4% and 9.3% in our series, respectively. Interestingly, similar to Perez et al,[25] we also found $iMLS_B$ phenotype in an isolate with intermediate resistance to erythromycin.

Unlike some other reports,[26,27] this study indicated that the incidence of $iMLS_B$ phenotype in MS-CoNS isolates was higher than that of MR-CoNS. Nevertheless, MR-CoNS showed higher rates of MS and $cMLS_B$ phenotypes. Additionally, although $iMLS_B$ phenotype was more prevalent among contaminants (9.3%), comparing to invasive ones (8.4%), the difference was not statistically significant.

In spite of the fact that isolates included in this study were collected from two geographically distinct hospitals, but unexpectedly, no significant differences were seen between these hospitals, neither in distribution of $iMLS_B$ phenotype nor in the resistance to other antibiotics. This event may be due to the included patients who were ranged in the same age group.

In our study, the total prevalence of MS and $iMLS_B$ phenotypes was approximately similar, that is, for almost each isolate with MS phenotype, there is an isolate showing inducible resistance. Given these data, the performance of D-test is strongly recommended in pediatric patients in our region.

In conclusion, having knowledge about the status of resistance in CoNS isolates will help to select proper antibiotics and take preventive measures to control resistance dissemination in the hospital settings. Additionally, rapid and accurate detection of $iMLS_B$ phenotype using the simple D-test will save time for clinicians, and treatment failure due to conversion resistance during clindamycin therapy can be avoided.

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