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Evaluation of Sensitivity of Commonly used Antibiotics in Staphylococcus Epidermidis Clinical Isolates From Assir Region, Saudi Arabia

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Result: 58 Staphylococcus epidermidis clinical isolates including 14 diabetics. Age groups include 29 (0-15yrs), 14 (16-50yrs) and 15 (50yrs& above). The total resistance cases to Oxacillin/ Mithicillin was found to be 56 cases (96.4%); all non diabetics were resistance. Resistance and sensitivity to Ciprofloxacin among diabetic and non diabetic were 75.9% and 24.1% respectively. Total resistance to Fusidin were 81%, while total resistant to Erythromycin in all ages groups were 86.2%. In age group (0-15) years 93.1% were resistant to the drug which comprises, 54% of the total resistant cases (n=50) and 46.6% from all Staphylococcus epidermidis cases (n=58).

Conclusion: Staphylococcus epidermidis is a pathogen associated with community acquired and nosocomial infections. The nosocomial infections are predominant in neonatal intensive care units (NICU). Resistance of Erythromycin in S. epidermidis cases among children is highly observed as this drug is commonly used by this age group. Diabetes has equivocal effect on drugs sensitivity. The frequency of staphylococcus multi-drugs resistance is rising.

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I. Introduction

Friedrich Julius Rosenbach distinguished S. *epidermidis* from S. *aureus* in 1884, initially naming S. *epidermidis* as S. *albus.* He chose *aureus* and *albus* since the bacteria formed yellow and white colonies, respectively. S. *epidermidis* causing nosocomial and community acquired infections [1]

S. *epidermidis* is a very hardy microorganism, consisting of nonmotile, Gram-positive cocci, arranged in grape-like clusters. It forms white, raised colonies approximately 1–2 millimeter in diameter after overnight incubation, and is nonhemolytic on blood agar. It is a catalase-positive, coagulase-negative, facultative anaerobe that can grow by aerobic respiration or by fermentation. Some strains may not ferment [2].

Biochemical tests indicate this microorganism also carries out a weakly positive reaction to the nitrate reductase test. It is positive for urease production, is oxidase negative, and can use glucose, sucrose, and lactose to form acid products. In the presence of lactose, it will also produce gas. *S. epidermidis* does not possess the gelatinase enzyme, so it cannot hydrolyze gelatin. It is sensitive to novobiocin, providing an important test to distinguish it from *Staphylococcus saprophyticus*, which is coagulase-negative, as well, but novobiocin-resistant. Similar to those of *Staphylococcus aureus*, the cell walls of *S. epidermidis* have a transferrin binding protein that helps the organism obtain iron from transferrin. The tetramers of a surface exposed protein, glyceraldehyde-3-phosphate dehydrogenase, are believed to bind to transferrin and remove its iron. Subsequent steps include iron being transferred to surface lipoproteins, then to transport proteins which carry the iron into the cell [3] [3]. The normal practice of detecting *S. epidermidis* is by using the Baird-Parker agar with egg yolk supplement. Colonies appear small and black. They can be confirmed using the coagulase test. Increasingly, techniques such as real-time PCR and

quantitative PCR are being employed for the rapid detection and identification of *Staphylococcus* strains [4][4]. Normally, sensitivity to desferrioxamine can also be used to distinguish it from most other staphylococci, except in the case of *Staphylococcus hominis*, which is also sensitive. In this case, the production of acid from trehalose by *S. hominis* can be used to tell the two species apart.

Resistance to antimicrobial agents (AMR) has resulted in morbidity and mortality from treatment failures and increased health care costs. Although defining the precise public health risk and estimating the increase in costs is not a simple undertaking, there is little doubt that emergent antibiotic resistance is a serious global problem. Appropriate antimicrobial drug use has unquestionable benefit, but physicians and the public frequently use these agents inappropriately.

Aseer Central Hospital is almost 600 bedded and it is accredited from The Central Board of Arab Health. It's laboratory is a regional referral hub. The other hand, the hospital is affiliated to the medical college of king Khalid University. This study aimed at evaluating the commonly used antibiotics resistant and the factors affecting the drugs sensitivity of Staphyloccocus epidermidis isolates from nasal swabs of patients presented at Aseer Central Hospital General Lab.

II. Material and Methods

The patients in this study were informed about the study content and procedures with preservation of human rights in concordance with the research ethics of the Deanship of Scientific Research and Research Center For Medical *College,* King Khalid University, Kingdom of Saudi Arabia.

A total of 58 clinical isolates including; respiratory infection, central nervous system infections, urogenital infection, musculoskeletal (Joints) infections and skin infection were included. Blood, urine and swabs (nasal, skin and conjunctivae) specimens have been tested by bacteriology, chemical and PCR Assay. Bacteriology procedures ; staining, culture, catalase, coagulase and antibiotics sensitivity test using diffusion disc test, minimum inhibitory concentration (MIC) [5] and molecular (PCR) for confirmation of Staphylococcal species [6] and detection of the Mec A gene [7]. General primers for detection of positive Staphylococcal isolates not carrying the Mc Agene were used. The codes and sequences of the primers (50 pmol of primer per reaction) were as follows: ERIC-1R, 59-ATG TAA GCT CCT GGG GAT TCA C-39; ERIC-2, 59-AAG TAA GTG ACT GGG GTG AGC G-39; (*Staphylococcus epidermidis* ATCC 12228 chromosome, complete genome NCBI Reference Sequence: NC_004461.1). The PCR mixture was overlaid with 5 ul of mineral oil to prevent evaporation. Amplification of DNA fragments was performed in a Biomed thermo-cycler (model 60; Biomed, Theres, Germany) with predenaturation at 94C° for 4 min, followed by 40 cycles of 1 min at 94C°, 1 min at 55C°, and 2 min at 74 C°. Amplicons were analyzed by agarose gel electrophoresis containing 1% agarose (Hispanagar; Sph. Leiden, The Netherlands) in 0.53 Tris-borate-EDTA (TBE) in the presence of ethidium bromide (0. 0.3 mg/ml) at a constant current of 100 mA for 1 h.

a) Statistical Study

Clinical and Laboratory data were recorded in special formats and entered in stat computer program (SPSS). Descriptive and analytical statistical analysis were performed and final results were plotted in tables.

III. Results

58 *Staphylococcus epidermidis* and negative Mec A gene clinical isolates including 14 diabetics. Age groups include 29 (0-15yrs), 14 (16-50yrs) and 15 (50yrs& above). 29 patients (50%) have presented with skin sepsis this due to the fact that *S. epidermidis* is a known normal flors of the skin. Distribution of patients according to their sex and diagnosis . Table 1.

Distribution of patients according to their presence in hospital revealed that; 35 patients were in intensive care units and 24 patients were in PICU and NICU (Pediatric and Neonates). Table 2.

The total resistance cases to Oxacillin/ Mithicillin was found to be 56 cases (96.4%); 12 diabetic patients (21.4%) and 44 non diabetic (78.6%). So all non diabetics were resistance. Table 3.

Resistance and sensitivity to Ciprofloxacin in all 58 *Staphylococcus epidermidis* diabetic and non diabetic patients under study were 75.9% and 24.1% respectively. Table 4.

Total resistance to Fusidin were 47 cases (81%) and total sensitivity to Fusidin were 11 cases (19%). Table 5

Total resistant and sensitivity to Erythromycin in all ages groups were 86.2% and 13.8% respectively. In age group (0-15) years 93.1% were resistant to the drug which comprises, 54% of the total resistant cases (n=50) and 46.6% from all *Staphylococcus epidermidis* cases (n=58). Table 6.

Table 1 : Distribution of patients according to their sex and diagnosis

Diagnosis	Sex		Total
	Male	Female	
Acute Abdomen	0	1	1
Sepsis	**18**	**11**	**29**
URI	2	0	2
Post Surgery	0	1	1
CVA	4	3	7
ESRD	1	0	1
RDS	1	0	1
PUO(Pyrexia)	1	0	1
ELEC Burn	1	0	1
Trauma	1	1	2
RTA	7	0	7
Head Inj.	1	1	2
DM	2	1	3
Total	39	19	58

Table 2 : Distribution of patients according to age group in different departments

Department	Age			Total
	(0- 15)years	(16 – 50) years	51 years and more	
OPD	2	4	2	8
MMW	0	0	1	1
MFSW	1	0	0	1
MSW	1	0	2	3
FMW	0	1	2	3
PMW	1	0	0	1
ER	1	1	0	2
PICU	**15**	**1**	**0**	**16**
MOW	0	0	1	1
ICU	0	2	2	4
IMCU	0	2	4	6
CCU	0	0	1	1
NICU	**8**	**0**	**0**	**8**
BU	0	1	0	1
MNW	0	1	0	1
MUW	0	1	0	1
Total	29	14	15	58

Table 3 : Crosstabs showed Oxacillin/ Mithicillin sensitivity and resistance in *Staphylococcus epidermidis* positive cases among diabetics and non diabetics

Antibiotic sensitivity profile			Diabetes mellitus		Total
			Yes	No	Yes
Oxacillin/ Mithicillin	R	Count	12	44	56
		% within Oxacillin/ Mithicillin	21,4%	78,6%	100,0%
		% within Diabetes mellitus	85,7%	100,0%	96,6%
		% of Total	20,7%	75,9%	96,6%
	S	Count	2	0	2
		% within Oxacillin/ Mithicillin	100,0%	,0%	100,0%
		% within Diabetes mellitus	14,3%	,0%	3,4%
		% of Total	3,4%	,0%	3,4%
Total		Count	14	44	58
		% within Oxacillin/ Mithicillin	24,1%	75,9%	100,0%
		% within Diabetes mellitus	100,0%	100,0%	100,0%
		% of Total	24,1%	75,9%	100,0%

Table 4 : Crosstabs showed Ciprofloxacin sensitivity and resistance in *Staphylococcus epidermidis* positive cases among diabetics and non diabetics

Antibiotic sensitivity profile			Diabetes mellitus		Total
			Yes	No	Yes
Ciprofloxacin	R	Count	10	34	44
		% within Ciprofloxacin	19,5%	80,5%	100,0%
		% within Diabetes mellitus	57,1%	75,0%	70,7%
		% of Total	13,8%	56,9%	70,7%
	S	Count	4	10	14
		% within Ciprofloxacin	28,6%	71,4%	100,0%
		% within Diabetes mellitus % of Total	28,6% 6,9%	22,7% 17,2%	24,1% 24,1%
	Total		14 24.1%	44 75.9%	58 100%

Table 5 : Crosstabs showed Fusidin sensitivity and resistance in *Staphylococcus epidermidis* positive cases

Antibiotic sensitivity profile			Diabetes mellitus		Total
			yes	no	
Fusidin	R	Count	11	36	47
		% within Fusidin	18,5%	81,5%	100,0%
		% within Diabetes mellitus	78.5%	81.8%	81%
		% of Total	18.9%	62.1%	81%
	S	Count	3	8	11
		% within Fusidin	27,3%	72,7%	100,0%
		% within Diabetes mellitus	21,4%	18,2%	19,0%
		% of Total	5,2%	13,8%	19,0%
	Total		14 24.1%	44 75.9%	58 100%

Table 6 : Crosstabs showed Erythromycin sensitivity and resistance in *Staphylococcus epidermidis* positive cases among different age groups

Antibiotic sensitivity profile			age group			Total
			0-15	16-50	51+	
Erythromycin	R	Count	27	11	12	50
		% within Erythromycin	54 %	22 %	24 %	100,0%
		% within age group	93,1%	78,6%	80 %	84,5%
		% of Total	46,6%	19,0%	19,0%	86,2%
	S	Count	2	3	3	8
		% within Erythromycin	25,0%	37,5%	37,5%	100,0%
		% within age group	6,9%	21,4%	20,0%	13,8%
		% of Total	3,4%	5,2%	5,2%	13,8%
Total		Count	29	14	15	58
		% within Erythromycin	50,0%	24,1%	25,9%	100,0%
		% within age group	100,0%	100,0%	100,0%	100,0%
		% of Total	50,0%	24,1%	25,9%	100,0%

IV. Discussion

Staphylococcus epidermidis is one of 33 known species belonging to the genus *Staphylococcus*. The taxonomy of this bacteria is; Kingdom: Bacteria. Phylum: Firmicutes. Class: Cocci. Oreder: Bacillales. Family: Staphylococcaceae. Genus: Satphylococcus. Species: S. epidermidis. It is part of human skin flora (commensal), and consequently part of human flora. It can also be found in the mucous membranes and in animals. Due to contamination, it is probably the most common species found in laboratory tests [8][7]. Although *S. epidermidis* is not usually pathogenic, patients with compromised immune systems are often at risk for developing an infection. These infections can be both nosocomial or community acquired, *S. epidermidis* is also a major concern for people with catheters or other surgical implants because it is known to cause biofilms that grow on these devices [9][8]. *S. epidermidis* causes biofilms to grow on plastic devices placed within the body [10][9]. This occurs most commonly on intravenous catheters and on medical prostheses. Infection can also occur in dialysis patients or anyone with an implanted plastic device that may have been contaminated. Another disease it causes endocarditis [11]. In some other cases, sepsis can occur in hospital patients. Resistant organisms are most commonly found in the intestine, but organisms living freely on the skin can also become resistant due to routine exposure to antibiotics secreted in sweat [12][12]. Detection of the mecA gene by polymerase chain reaction (PCR) is the gold standard for identifying methicillin-resistant Staphylococcus aureus (MRSA). PCR assays, employing MR1-MR2 primers (primer set 1) and MR3-MR4 primers (primer set 2) to generate 154 and 533 bp fragment, respectively, are most widely used for amplification of mecA gene [13][13].Spread of *S.* spp. (including MRSA) generally is through human-to-human contact, although recently some veterinarians have discovered the infection can be spread through pets, with environmental contamination. Cases of *S.* spp. Nosocomial infections have reported to be transported by polyester, the main material used in hospital curtains in hospitals across America [14][14]. An important and previously unrecognized means of community-associated MRSA colonization and transmission is during sexual contact [15][15]. It was discovered that there are two different strains of S. epidermidis, one that inhibits biofilm formation by S. aureus, S. epidermidis strain JK16 (inhibitory type), and one that does not (non-inhibitory type) S. epidermidis strain JK11 [16][16]. Staphylococcal resistance to penicillin is mediated by penicillinase (a form of β-lactamase) production: an enzyme that cleaves the β-lactam ring of the penicillin molecule, rendering the antibiotic ineffective. Penicillinase-resistant β-lactam antibiotics, such as methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, and flucloxacillin, are able to resist degradation by staphylococcal penicillinase. Resistance to methicillin is mediated via the *mec* operon, part of the staphylococcal cassette chromosome mec (SCC*mec*). Resistance is conferred by the *mecA* gene, which codes for an altered penicillin-binding protein (PBP2a or PBP2') that has a lower affinity for binding β-lactams (penicillins, cephalosporins, and carbapenems). This allows for resistance to all β-lactam antibiotics, and obviates their clinical use during MRSA infections. As such, the glycopeptide vancomycin is often deployed against MRSA [17][17]. Aminoglycoside antibiotics, such as kanamycin, gentamicin, streptomycin, etc., were once effective against staphylococcal infections until strains

evolved mechanisms to inhibit the aminoglycosides' action, which occurs via protonated amine and/or hydroxyl interactions with the ribosomal RNA of the bacterial 30S ribosomal subunit [18][18]. There are three main mechanisms of aminoglycoside resistance mechanisms which are currently and widely accepted: aminoglycoside modifying enzymes, ribosomal mutations, and active efflux of the drug out of the bacteria [19][19]. MRSA infections in both the hospital and community setting are commonly treated with non-β-lactam antibiotics, such as clindamycin (a lincosamine) and co-trimoxazole (also commonly known as trimethoprim/ sulfamethoxazole). Resistance to these antibiotics has also led to the use of new, broad-spectrum anti-Gram-positive antibiotics, such as linezolid, because of its availability as an oral drug. So it is nowadays highly recommended to use combined therapy to treat severe cases of S. aureus infections such as pneumonia, meningitis and toxic shock syndrome [20].[20].All 29 S. epidermidis isolates were found to be resistant to oxacillin and were positive for the mecA gene. The isolates showed several multidrug-resistance patterns; the resistance rates to gentamicin, erythromycin, clindamycin, and [21]were susceptible to vancomycin, teicoplanin, rifampin, synercid, and ciprofloxacin. Several genotypic and phenotypic patterns were detected among the S. epidermidis isolates: antibiogram typing showed seven different patterns, one of which was shared by 65% of the isolates, whereas the most prevalent RAPD genotype was shared by only five S. epidermidis isolates [22], and did not correlate with antibiotic resistance phenotype. The diverse clonal origin of tested isolates indicates the presence of multiple S. epidermidis strains among neonates in the NICU setting [23][21]. In another study the nasal carriage of methicillin-resistant coagulase-negative staphylococci (MR-CoNS) is highly prevalent in community subjects [24][22]. Few studies on staphylococcal infections and drugs sensitivity were conducted in Saudi Arabia [25] [26] [27][24, 25, 26]. Resistance is conferred by Penicillinase-resistant β-lactam antibiotics and the mec A gene, which codes for an altered penicillin-binding protein (PBP') that has a lower affinity for binding β-lactams (penicillins, cephalosporins, and carbapenems). This allows for resistance to all β-lactam antibiotics, and obviates their clinical use during MRSA infections. Mec A gene is known associated factor of drug resistance for Oxacillin/Mithcillin drug as all isolates were Mec A gene negative, the resistance could be explained by the thick biofilm caused by this bacteria which guard against drug penetration [28] [29],

V. Acknowledgement

We confer our gratitude to the laboratory of Assir Central Hospital. Our sincere thanks to the department of microbiology, College of Medicine, King Khalid University (Saudi Arabia) and Ribat National University (Sudan).

VI. Conclusion

Staphylococcus epidermidis is a pathogen associated with community acquired and nosocomial infections. These infections were predominant among children in neonatal intensive care units (NICU) .

Resistance of Erythromycin in *S. epidermidis* cases among children is highly observed as this drug is commonly used by this age group.

Diabetes has equivocal effect on drugs sensitivity. The frequency of staphylococcus multi-drugs resistance is rising as well in Asser region), involving variable drugs mode of actions; cell wall inhibitors, protein synthesis inhibitors and DNA gyrase inhibitors.

Rising of multidrug resistance could be attributed to genetic clone and the adherence of the pathogen to devices like ventilators and catheters .

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