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OUTCOME OF IMPLEMENTATION OF HOSPITAL INFECTION CONTROL GUIDELINES ON THE ANTIBIOTIC RESISTANCE PATTERN IN *STAPHYLOCOCCUS AUREUS* ISOLATED FROM SKIN AND SOFT TISSUE INFECTIONS: A RETROSPECTIVE TWO TIME POINT STUDY

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ABSTRACT: BACKGROUND: Skin and soft tissue infections (SSTIs), by *Staphylococcus aureus* is a commonly observed phenomena. However, when the organism is methicillin-resistant *S. aureus* (MRSA) the morbidity is high and the organism can also lead to death of the individual if immunocompromised. Treatment of MRSA involves use of high end drugs that are extremely expensive and accompanied by side effects. METHODS: This is a retrospective study and the medical records for the year 2010 and 2015 for *S aureus* in SSTIs were accessed. The two time points were selected because in the beginning of the decade Hospital Infection control was upgraded and emphasized through rigorous sensitization and implementation audits. The incidence and drug resistance pattern for various clinically used antibiotics against *S aureus* at two time points were analyzed. RESULTS:The results indicated that there was a 23.24% decrease in the incidence of MRSA and was significant ($p< 0.019$). However there was an increase in resistance of S aureus to fluoroquinolones and macrolides ($p< 0.0001$).CONCLUSIONS: The safety measures adopted has immense use in reducing hospital infection and be of use to public health. This study indicates that adoption of hospital infection control measures by regular practice of the stipulated guidelines is an important way in reducing the incidence of MRSA infection.

KEY WORDS: *Staphylococcus aureus;* MRSA; Hospital Infection Control; Skin and soft tissue infections.

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INTRODUCTION:

Skin and soft tissue infections (SSTIs), also termed as skin structure infections is an important common medical condition, and needs immediate medical attention and care. [1,2] From a classification perspective, SSTIs are grouped as purulent infections (e.g., furuncles, carbuncles, and abscesses) and non purulent infections (e.g., erysipelas, cellulitis, necrotizing fasciitis) and on the degree of severity further as mild, moderate, and severe. [2] The mild infections normally manifest as local symptoms, while the moderate to severe infections also involves systemic effects that manifest as sepsis with fever, spurt in the number of WBC cells, increased heart rate and or higher respiratory rate.[1,2]

In most cases, bacteria are responsible for the SSTIs and report indicates that the very prevalent gram-positive cocci *StaphylococcuS aureus* (SA)is the causative agent.[3] Historically, *S aureus* were very well controlled by administration of penicillin.[1] However, the rampant injudicious use of antibiotics had lead to evolution of *S aureus* that are today resistant not only to pencillin but also for subsequent antibiotics like methicillin a semisynthetic penicillinase-resistant antibiotic introduced and found to be effective against *S aureus* in the early 1960s [2,4]. The *S aureus* that are resistant to the drug methicillin are now termed as methicillin-resistant *S. aureus* (MRSA).[2,4,5]

From a clinical perspective, the spread of MRSA is alarming as the therapeutic outcome of infections resulting from MRSA is worse when compared to that of the methicillin-sensitive strains.[2,6] Global data affirms that Infections due to MRSA causes significant morbidity and mortality especially among the immunocompromised and the weak.[5] MRSA is increasing worldwide, and in various parts of India.[7-19] Under these circumstances the development of antibiotics like vancomycin, teicoplanin and linezolid has been observed to be beneficial. However their use is associated with untoward side effects and is expensive for the patient and the hospital.

In lieu of these observations, the Centre for Disease Control and Prevention (CDC) has recommended that a close monitoring of the resistance pattern of the *S. aureus* is the need of the hour to map and combat the emergence of the resistant pathogen.[20,21] In accordance to the tenets of the recommendation, the present study was conducted to observe if there is any change in the sensitivity pattern of *S aureus* isolated from the SSTI patients in the year 2010 and 2015 at a tertiary care hospital.

MATERIAL AND METHODS:

This was a retrospective study and was carried out in the department of Hospital Infection Control Unit of the Clinical Microbiology of Father Muller Medical College Hospital. The data on the antibiotic sensitive pattern of the *Staphylococcus aureus* isolated from the skin and soft tissue infections were studied for 2010 and 2015. The data was collected from Hospital database after obtaining the necessary permission from the Institutional ethics Committee.

The sensitive pattern for the following antibiotic was collected from the database: Ampicillin (10µg) Amoxyclav (20/10 µg), Cephalexin (30 µg), Cefoxitin (30 µg), Cotrimoxazole (1.25/23.75 µg), Gentamicin (10 µg), Amikacin (30 µg), Ciprofloxacin (5 µg), Levofloxacin (5 µg), Azithromycin (15 µg), Clindamycin (2 µg), Vancomycin (30 µg), Linezolid (30 µg), Teicoplanin (30 µg) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[22]

The drug resistance pattern for each of the isolate was entered in the Microsoft Excel, coded and then subjected to statistical analysis for the incidence of resistance for every antibiotic tested. Additionally data was also sorted taking in to consideration the pharmacological class/type they belonged to. The data were analyzed by x^2 for each antibiotic tested. In addition to this the mean was calculating

considering the number of resistance possessed by each against each drug, as well as for the class the antibiotic belonged to by using unpaired students *t* test. A statistical value of $p < 0.05$ was considered significant.

RESULTS:

The study indicates that a total of 735 and 776 *S aureus* organisms were isolated from the SSTIs were isolated and tested against a panel of antibiotics in accordance to the CLSI guidelines. The most important observation was all the organisms tested in both the years were sensitive to vancomycin, linezolid and teicoplanin. The results of resistance to the various antibiotics and grouped in accordance to the chemical class are depicted in Table 1 and 2.

With respect to the data when analyzed from the perspective of individual antibiotics, the results indicated that when compared to the year 2010 there was decrease in the percentage of S aureus resistant to A (87.21 vs 83.39), CP (45.85 vs 14.93), CN (19.45 vs 14.93), CO (47.89 vs 30.75), G (32.78 vs 26.38) ($P < 0.02$ to 0.0001). On the contrary, during the study time points there was increase in the number of organisms resistant to AK (2.31 vs 7.07), OF (41.49 vs 62.16), LF (22.44 vs 32.43), E (20.40 vs 42.59) and CD (3.67 vs 17.11) ($P < 0.0001$). The data are all represented in Table 1.

When the data was analyzed from the perspective of the class the antibiotics belonged to, the results indicated that when compared to the year 2010 there was decrease in the percentage of *S aureus* resistant to the beta lactams ($p < 0.0001$), folic acid inhibitors ($p < 0.0001$), aminoglycoside ($p < 0.6$), while on the contrary there was a increase in resistance to fluoroquinolones ($p < 0.0001$) and macrolides ($p < 0.0001$). It was also observed that there was a 23.24% reduction in the incidence of MRSA. However a cumulative analysis for all the 11 antibiotics tested indicated that when compared to the year 2010, the number of organism resistant to the antibiotics increased from 3.47±1.19 (in 2010) to 3.71±2.39 (in 2015) and was significant ($p < 0.04$) (Table 2).

DISCUSSION:

Innumerable data published from around the world have equivocally shown that *S. aureus,* especially the MRSA, is a major pathogen especially amongst vulnerable at risk patients and also that their characteristics are changing rapidly.[23] The SSTIs are one of the most common infections by *S aureus* and the emergence of MRSA has compelled the use of fusidic acid, cotrimoxazole, clindamycin, tetracycline, rifampicin, quinolones, chloramphenicol, vancomycin, teicoplanin and linezolid.[24]

In this study it was observed that all the organisms tested in both the years were sensitive to vancomycin, linezolid and teicoplanin. However the drug resistant pattern changed significantly over a 5 year time period for most other antibiotics. The incidence of S. aureus resistant to the antibiotics like A, CP, CN, CO and G reduced while that for AK, OF, LF, E and CD increased. Additionally from the chemical classification perspective, a decrease in the percentage of S aureus resistant was seen for beta lactams, folic acid inhibitors, aminoglycoside, while on the contrary there was an increase in resistance to fluoroquinolones and macrolides (Table 1 and 2).

In our study it was observed that the pattern of drug resistance for *S aureus* was different in the two time points (Table 1 and 2). The most important aspect to be observed is that there was a 23.24% decrease in the incidence of MRSA and 35.79% reduction in resistance to the Folic acid inhibitor CO (Table 1, 2). With respect to aminoglycoside antibiotics there was a 19.53% reduction in resistance to G while for AK a 3.06 fold increase in the resistance was seen (Table 1). The reason for this change is that the Infection Control practices were implemented and monitored by the committee through regular sensitization, teaching and evaluation programs.

Table 1: Drug Sensitivity pattern of various antibiotics for *S aureus* tested in the year 2010 and

		Beta lactams				Folic acid inhibitor	Amino glycosides		Fluro quninolones		Macrolides	
		A	AC	CP	CN	CO	G	AK	OF	LF	E	CD
2010	Resistant	641	191	337	143	352	241	17	305	165	150	27
	Sensitive	94	544	398	592	383	494	718	430	570	585	708
	% Resistant	87.21	25.98	45.85	19.45	47.89	32.78	2.312	41.49	22.44	20.4	3.67
2015	*Resistant*	648	294	116	116	239	205	55	483	252	331	133
	Sensitive	129	483	661	661	538	572	722	294	525	446	644
	% Resistant	83.39	37.84	14.93	14.93	30.75	26.38	7.078	62.16	32.43	42.59	17.11
X^2 value		4.36	172.09	172.09	5.45	46.56	7.45	18.91	64.65	19.12	85.75	72.16
P value		0.036	0.0001	0.0001	0.019	0.0001	0.006	0.0001	0.0001	0.0001	0.0001	0.0001

Table 2: Drug Sensitivity pattern of various types of antibiotics on S aureus tested in the year 2010 and 2015

	2010	2015	p	t
Beta lactams (4)	1.78±0.49	1.52±1.20	<0.0001	4.25
Folic acid inhibitor (1)	0.47±0.51	0.31±0.46	<0.0001	6.89
Aminoglycosides (2)	0.35±0.51	0.33±0.59	0.6	0.51
Fluroquinolones (2)	0.62±0.81	0.90±0.78	<0.0001	-6.57
Macrolides (2)	0.23±0.48	1.18±0.74	<0.0001	-9.82
Total (11)	3.47±1.19	3.71±2.39	0.044	-2.01

These observations are in agreement to the previous reports of Tinelli and associates (2009) who have also observed that implementation of hospital infection control lead to a decline in the incidence of MRSA.25On the contrary, the resistance to aminoglycoside AK, the Fluroquninolones OF and LF and Macrolides E and CD increased by 2.08 and 4.66 folds respectively (Table 1). These observations are in congruence to reports published from around the world for these classes of antibiotics for S aureus.26-29 S. aureus is reported for its remarkable propensity to resist the effects of various antibiotics. In fact, the resistant strains of S aureus colonize, at times to spurt in to epidemic proportions. The unnerving ability of S aureus to asymptomatically colonized in normal individuals to become nasal carriers and the direct skin to skin contact mode of transmission increases susceptibility to infections. S aureus shows hyper virulence behavior due to selective pressure of antibiotics and horizontal/vertical gene transmission making it a formidable adversary in clinical management.24With respect to the mechanisms of drug resistance seen in S aureus reports indicate that for the antibiotic aminoglycoside, the resistant organisms have been shown to produce microbial enzymes the aminoglycosidase that inactivate the drug and reduce the affinity of the drug to the bacterial

ribosomes by inducing conformational changes of the bacterial binding site.[30] For the macrolides like ketolides and azalides, resistant strains of *S aureus* are reported to up regulate genes that mediate the active efflux of antibiotics by the pumps on bacterial cell membrane.[30] Additionally reports also indicate that in some *S aureus* strains resistance is also conferred to macrolides by genetically coded inducible constitutive enzymes to protect the ribosome from the macrolide attacks or by 50s ribosome.[30] With respect quinolones reports exists that *S aureus* develop drug resistance by causing chromosomal mutations to the DNA gyrase and Topoisomerase IV thereby altering the subunit binding site.[30] with fluoroquinolones, indicate that resistance occurs by altering the target site and reducing drug concentration within cell by altering permeability of bacteria. A similar mechanism/s must have occurred in these organisms.

CONCLUSION:

The present study demonstrated that excluding vancomycin, linezolid and teicoplanin, the drug resistance pattern at the time point studied varied for the clinically used antibiotics. The major limitation of this study is that this is a monocentric study and efforts are on to include multiple institutes/hospitals in the endeavor. On a positive note the most important aspect was that the implementation of Hospital infection control policy and its adherence led to a significant decrease in the percentages of MRSA in the latter time point. This clearly indicates that Hospital infection control programme is indeed an effective way to mitigate and control MRSA and is in congruence to the CDC guidelines and recommendations. Prospective studies are proposed in these lines as this will help us understand the magnanimity and pattern of drug resistant *S aureus* in the study area.

The other most important observation that brought to our knowledge was that the resistance to the commonly used effective drugs like the aminoglycoside AK, the fluoroquinolones (OF and LF); and the macrolides (E and CD) increased. The possible explanation for this is that in the recent past these drugs have been the cornerstone in treating infections and their rampant prescription without having an antibiogram results by the professionals and non-adherence to the dose and schedule, and over the counter prescription must have led to the resistant strains. Efforts have already been initiated towards remedial measures and on adherence to the good practice guidelines and antibiotic policy to minimize the evolution of drug resistant strains.

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