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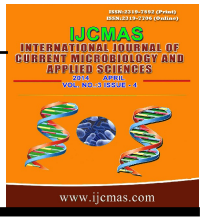

Original Research Article

Mupirocin Resistance in Surgical Intensive Care Unit

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A B S T R A C T

The aim of this study was to detect the incidence of surgical site infection, the prevalence of nasal carriage of MRSA in surgical intensive care unit(SICU) and to detect presence of mupirocin resistance in patients and health care workers.71 nasal, 71axillary and 34 wound swabs obtained from 71 patients in SICU of El-Demerdash Hospital(a tertiary care university hospital) were included in this study. The study also included 30 nasal and 30 interdigital swabs obtained from health care workers in SICU .All swabs were cultured on blood agar and ChromID™ MRSA agar media .Mupirocin resistance was detected using agar based susceptibility disc assay and E-test. Among all the MRSA isolates obtained from patients 78.9% were sensitive to mupirocin, 5.3% low level resistance and 15.8% were high level resistance.100% of MRSA isolates were sensitive to mupirocin. The incidence of surgical site infection in SICU was 21.12% and the incidence of MRSA surgical site infection in SICU was 2.81%. The prevalence of MRSA nasal colonization in patients was 33.8%. Nasal colonization with MRSA is more than that of axillary and wound. Our study revealed that mupirocin resistance is affected by gender, smoking, polytrauma, and combined infection.

Keywords

Mupirocin, MRSA, SICU, nasal colonization, surgical site infection.

Introduction

Carriage of Staphylococcus aureus in the nasal passages appears to play a key role in the epidemiology and pathogenesis of infection. Colonizing strains may serve as endogenous reservoir for overt clinical infections or may spread to other patients (Halablab et al., 2010).

Outbreaks of MRSA in the surgical intensive care units (SICU) are often prolonged and can result in substantial morbidity and mortality (Khan et al., 2009). Mupirocin is a topical antibiotic that inhibits bacterial isoleucyl tRNA sythetase, blocking the formation of isoleucyl tRNA, which in turn impairs bacterial protein synthesis (Theodore et al., 2007).

Intranasal application of mupirocin is used widely to eliminate S. aureus colonization and has been studied as a means of preventing health care associated

staphylococcal infection (Theodore et al.,2007).There are several other agents on the horizon that are under investigation and have potential for use as future agents for MRSA decolonization as follows: lauric acid monoester, lysostaphin, omiganan pentahydrochloride, probiotics, photodynamic therapy, bacteriophage approach (Abad et al.,2013)**.**

At least two forms of mupirocin resistance are known to occur in S. aureus. Low-level resistance characterized by a minimal inhibitory concentration(MIC) of 8 to 256 ug/ml, and high-level resistance, characterized by a MIC of ≥256 ug/ml (Shoham et al.,2010)**.**

High-level mupirocin resistance may be detected either by the agar-based susceptibility disc assay or the mupirocin E-test can also be detected using mupA targeted polymerase chain reaction (PCR) or with the broth micro dilution assay (Shoham et al.,2010).

The aim of the work is to detect the incidence of surgical site infection and the prevalence of nasal carriage of MRSA in the surgical intensive care unit and to detect presence of mupirocin resistance in patients and health care workers.

Materials and Methods

The present study was conducted at the Central Microbiology Laboratory, Department of Clinical and Chemical Pathology,Faculty of Medicine , Ain Shams University ,during the period from September 2012 to February 2013.

The study included 71nasal,71axillary and 34 wound swabs, that were obtained from71 patients admitted to surgical intensive care units in El-Demerdash hospital. The patients were 43 males and 28 females. Their ages ranged from 8 to 77 years.

The study included also 30 nasal 30 inter digital swabs obtained from 30 health care workers, working in the surgical intensive care units. They were 9 males and 21females.

Samples collection

Swabs of the patients were obtained from nose, surgical site infection and axillary area. Plain sterile cotton swabs (Shaanxi Longstar New Material Technology Co., China) were used. The patient's noses were disinfected from outside using 70% alcohol. Samples were taken from the anterior nares by gently rotating the swab over the mucosal surface of both nares.

Nasal and interdigital swabs of the health care workers were obtained. All Swabs were tranferred immediately to the microbiology laboratory for culture and sensitivity.

Materials used
Culture media

Blood agar (Oxoid, UK), ChromID™ MRSA agar medium (BioMerieux, Marcy l'Etoile, France).

Gram stain.

Antibiotic susceptibility

Mueller–Hinton agar (Oxoid, UK).
Mupirocin discs (Oxoid, UK).

Mupirocin E-test (BioMerieux, Marcy l'Etoile, France).

Methods used

Identification of organism by Culture on blood agar (colony morphology) and Microscopic examination with Gram stain

Detection of methicillin resistance using Culture on ChromID™ MRSA agar medium

The plates were incubated inverted at 37°C in aerobic conditions. The cultures were generally examined after 18-24 hours of incubation.

Detection of mupirocin resistance using Agar-based susceptibility disc assay

Disc diffusion tests were carried out according to the guidelines (CLSI, 2006).Plates containing Mueller–Hinton broth were swabbed in three directions with 0.5 McFarland inoculum and 6 mm discs containing 5 or 200µg mupirocin. Following incubation at 35°C for 18 hours, the diameters of the inhibition zones were determined in mm.

E-test

After overnight incubation a symmetrical inhibition ellipse is centered along the strip is formed .The MIC is read directly from the scale in term of µg/ml at the point where the edge of inhibition ellipse intersects the strip

Results and Discussion

The incidence of surgical site infection in the SICU was 21.12% and the incidence of MRSA surgical site infection in the SICU was 2.81%. The prevalence of MRSA colonization in the patient's nares was 33.8%.

Table (1) shows that 59.7% of nasal swabs were negative for MRSA and 40.3% were positive, 58.7% of axillary swabs were negative for MRSA and 41.3% were positive and 60% of wound swabs were negative for MRSA and 40% were positive.

According to Table (2) mupirocin sensitivity in nose was 79.3%, in axillary 77%and in wound 100%,low level resistance in nose was 0%, in axillary was 11.5 % and in wound was 0 % and high level resistance was 6% in nose, 3% in axillary and 0% in wound.

Among all studied patients 43.7% were sensitive to mupirocin 15.4% were resistant to mupirocin where as 40.9% had no MRSA infection as shown in Table 3.

Evaluating the role of risk factors, it was evident that resistance was more among males and smokers with statistically significant association by using Fisher Exact test. On the other hand no significant difference was found as regard age using Chi-square test. So mupirocin resistance was more common in males and smokers among different age groups as shown in Table (4).

There is statistical significant relation between types of isolates and resistance which was more among mixed infection by using Chi-square test and no significant statistical difference regarding the duration of hospitalization. So mixed infections by other isolates was associated with mupirocin resistance. While duration of hospitalization was not associated with mupirocin resistance as shown in Table (5).

Table (6) shows that majority of resistant cases were polytrauma with statistical

significant relation in between polytrauma and mupirocin resistance by using Chi-square test with p value<0.05.So the majority of resistant cases were polytrauma. Table (7) shows that mixed infections, polytrauma operation, male sex and smoking are ranked independent predictors of mupirocin resistance by Binary Logistic Regression. Where there were statistical significant relations between mupirocin resistance and mixed infections, polytrauma operation, male sex and smoking.

Among the 35 nasal swabs 81.4% were MSSA and 28.6 % were positive for MRSA and among the interdigital swabs 88.9% were MSSA 11.1% were MRSA as shown in Table(8).

Among the health care workers 100% of MRSA isolates were sensitive to mupirocin, while 0 % of isolates had a Low level resistance and 0% of isolates had high level resistance in both nasal and interdigital swabs of the health care workers as shown in Table (9).

In the present study the most common site for MRSA carriage is the anterior nares and this agreed with Halablab et al.,2010 who stated that carriage of S. aureus in the nasal passages appears to play a key role in the epidemiology and pathogenesis of infection. Graham et al.,2006who stated that in the largest population-based survey completed, they found that among 9622 National Health and Nutrition Examination Survey (NHANES) participants who underwent cultures of their nares, 31.6% were colonized with MSSA and 0.84% were colonized with MRSA. Generally between 30% and 50% of healthy adults have evidence of nasal colonization with MSSA, and up to 3% are colonized with MRSA.

The prevalence of mupirocin resistance among MRSA isolates in this study was that 5.3% were low level resistance and 15.8% were high level resistance and this agreed with Vivoni et al., 2005 who stated that previous reports of mupirocin resistance in patients with S.aureus have primarily been from institutions with high levels of resistance in the context of widespread mupirocin use, with rates of resistance ranging from 11.3% to 65%.And the rate of overall mupirocin resistance in our study population (15.3%) according to Jeffrey et al.,2007is on the higher end of the range of rates of resistance (4.6%–17.8%) and this did not agree with Summiya et al., 2011 where high level resistance was 0% and low level resistance was 1% and Andrew et al.,2007where high level resistance was 4% and low level resistance was 8% and Fitzory,2008 where high level resistance was 26.1% and low level resistance was 40.1%, and Choudhury et al., 2012 who stated that the overall prevalence of high level mupirocin resistance in a tertiary care hospital was 11%.

In the present study age of the studied population had no significant relation with mupirocin resistance and this agreed with Caffrey et al., 2010 who stated that age has no significant relation with mupirocin resistance and Tara et al., 2009 who stated that although 60% of mupirocin-resistant MRSA isolates were found in patients >60 years of age, it did not appear that increased age is a risk factor for mupirocin-resistant MRSA. However, Jeffrey et al., 2007 stated that patients with mupirocin-resistant MRSA were also significantly older than patients with mupirocin-susceptible MRSA.

In the present study sex has significant

relation with mupirocin resistance where the resistance rate was more among males as in Halablal et al., 2010 who stated that higher colonization rate of MRSA in males than females. In contrast to Caffrey et al., 2010 who stated that sex have no significant relation to resistance.

In the present study smoking had significant relation with mupirocin resistance where the resistance rate was more among smokers. This may be related to increase MRSA colonization as in Halablal et al., 2010 who stated that tobacco smoking appears to have a noticeable effect on the microbial ecology of the nose. Generally, smokers harbored a greater number of S. aureus and therefore MRSA. But this did not agree with Jann et al.,2009 who stated that smoking is a protective factor against S. aureus, not only specifically against MRSA colonization. Smoking might be a protective factor against the nasal colonization of S. aureus. It might be that smoking creates a microenvironment in the nose that protects against the growth of S. aureus.

In the present study mixed infection had significant relation with mupirocin resistance and this is related to the type of isolate where one of isolates was pseudomonas as in Caffery et al.,2010 who stated that mupirocin is an antibiotic produced by the Gram negative bacterium Pseudomonas fluorescens. As such, Pseudomonas is insensitive to mupirocin resulting from its inherited resistance to the antibiotic it produces. The mupA gene, which exists in both low- and high-level resistance, is unstable and the movement of mupA-mediated mupirocin resistance between plasmids exists between bacterial isolates. It is currently unknown whether *P. aeruginosa* is a carrier and potentially harbours the mupA gene compx. Also patients with mixed infection are likely to take more antibiotics which may select strains with mupirocin resistant MRSA as in Caffrey et al., 2010 who stated that the empiric exposures to antibiotics without MRSA coverage may select for MRSA exhibiting mupirocin resistance.

In the present study that majority of resistant cases were polytrauma with significant relation in between polytrauma and resistance and this agreed with Wilcox et al.,2003 Orthopedic units are classed as high-risk areas, because of the potentially serious consequences of MRSA infection, particularly in patients with prosthetic joints and patient with polytrauma usually has fractures. And this agreed with Omer and Meshref, 2008 who stated that the risk

Table.1 The number and percentage of Gram positive cocci by Gram stain and the result of growth on chromogenic agar of patients

Characters	Nasal swabs	Axillary swabs	Wound swabs
Gram stain			
Gram positive cocci	72 (85.7%)	63 (79.7%)	5(33.3%)
Chromogenic agar			
Negative	43 (59.7%)	37 (58.7%)	3(60%)
Positive (MRSA)	29 (40.3%)	26 (41.3%)	2(40%)

Table.2 Results of mupirocin susceptibility testing of patients.

	Nasal swabs	**Axillary swabs**	**Wound swabs**
Disc diffusion test			
Sensitive	23 (79.3 %)	20 (77 %)	2 (100 %)
Low level resistance	0 (0 %)	3 (11.5 %)	0 (0%)
High level resistance	6 (20.7 %)	3 (11.5 %)	0 (0%)
E-test			
Sensitive	23 (79.3 %)	20 (77 %)	2 (100 %)
Low level resistance	0 (0 %)	3 (11.5 %)	0 (0%)
High level resistance	6 (20.7 %)	3 (11.5 %)	0(0%)

Table.3 The distribution of MRSA carrier among the studied population as regard sensitivity

Variable	**No. of patients**		**%**
MRSA carrier	Sensitive	31	43.7%
	Resistance	11	15.4%
No MRSA carrier	29		40.9%

Table.4 Comparison between sensitive and resistant cases to Mupirocin as regard demographic data

Variables	**Mupirocin Sensitive(31)**	**Mupirocin Resistance(11)**	X^2	**P**
Age	48.5±4	49.1±3	0.6	>0.05 NS
Gender			Fisher	<0.05 S
Male	15(48.4%)	10(90.9%)		
Female	16(51.6%)	1(9.1%)		
Smoking			Fisher	<0.05 S
No	24(77.4%)	4(36.4%)		
Yes	7(22.6%)	7(73.6%)		

Table.5 Comparison between sensitive and resistant cases to Mupirocin as regard isolates in wound infection and duration of hospitalization

Variables	**Mupirocin Sensitive(31)**	**Mupirocin Resistance(11)**	X^2	**P**
Isolates				
Klebsiellaspp.	4(50%)	0		
MRSA	2(25%)	0	10	<0.05 S
Proteus spp.	1(12.5%)	0		
Acinetobacter&pseudomonas	0	1(50%)		
MRSA&E-coli spp.	1(12.5%)	0		
Klebsiella spp., MRSA & acinetobacter spp.	0	1(50%)		
Duration(mean±SD)	9.2±3	8.3±2	0.4	>0.05 NS

Table.6 Comparison between sensitive and resistant cases to Mupirocin as regard type of surgery

Variables	Mupirocin Sensitive(31)	Mupirocin Resistance(11)	X^2	P
Minor	1(3.2%)	0	12	<0.05 S
GIT	5(16%)	1(9%)		
CNS	10(32.2%)	2(18%)		
CVS	1(3.2%)	1(9%)		
Orthopedic surgery	5(16%)	1(9%)		
Polytrauma	7(22.6%)	5(45.5%)		
Urology	2(6.4%)	0		

Table.7 Different predictors of Mupirocin resistance by logistic regression model

Variables	Beta coefficient	P	Odd's(95%CI)
Mixed infection	0.78	<0.05	1.6(0.4-7)
Polytrauma	0.66	<0.05	1.5(0.3-6.8)
Male sex	0.45	<0.05	1.2(0.3-11.2)
Smokers	0.36	<0.05	1.1(0..1-8.9)

Table.8 The number and percentage of Gram positive cocci and the result of growth on chromogenic agar of health care workers

	Nasal swabs	Interdigital swabs
Gram stain		
Gram positive cocci	35 (100%)	9(81.8%)
Chromogenic agar		
Negative	25(81.4%)	8 (88.9%)
Positive (MRSA)	10(28.6%)	1 (11.1%)

Table.9 Results of mupirocin susceptibility testing of health care workers

	Nasal swabs	Interdigital swabs
Disc diffusion test		
Sensitive	10(100%)	1(100%)
Low level resistance	0(0%)	0(0%)
High level resistance	0(0%)	0(0%)
E-test		
Sensitive	10(100%)	1(100%)
Low level resistance	0(0%)	0(0%)
High level resistance	0(0%)	0(0%)

of acquiring MRSA in the ICU is increased by the severity of illness, length of stay, intravascular device use, and the intensity of exposure of infected patients to antibiotics.

In the present study exposure to mupirocin had no significant relation with mupirocin resistance and this agreed with Talon et al., 2011who stated that Mupirocin resistance is not an inevitable consequence of mupirocin use and Jeffrey et al.,2007 where a report from the US described a high rate of MRSA with mupirocin resistance in a surgical intensive care unit where mupirocin use was at a low level. However this did not agree with Fawley et al.,2006 who stated that prolonged, widespread or uncontrolled use, and multiple courses of mupirocin are all associated with the development of mupirocin resistance and Andrew et al.,2007 who stated that mupirocin resistance is often associated with the widespread use of mupirocin.

In the present study the rate of MRSA colonization in the nose of HCWs was 28.6% which agreed withWerner and Stephan, 2008 where they stated that MRSA colonization in nose of HCWs range 0–59%. In the present study the rate of MRSA colonization in the interdigital of HCWs was 11.1% which did not agree with Werner and Stephan, 2008 where they stated that MRSA colonization were 6·4% for hands. Our study revealed that mupirocin resistance is affected by gender, smoking, polytrauma, and combined infection. On the other hand, it is not affected by age, systemic diseases, skin infection, diabetes, wound infection, type of isolate, and antibiotic uptake.

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