Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 3069 – 3079
Received 05 March 2021; Accepted 01 April 2021.

Mupirocin Resistance among MethicillinResistant Staphylococcus Aureus Nasal Isolates from Health Care Workers; An Egyptian Single Centre Study

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Abstract:

Back ground: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major health concern in hospital environment. The isolates resistance to most previously used antibiotics is clearly escalating. In many hospitals, MRSA became mostly universal in the hospital environment. Health care workers (HCWs) can transmit MRSA from patient to patient by their contaminated hands, gloves, aprons and other instruments.

Aim of the Study:Our objective was to evaluate mupirocin resistance in nasal carriage of *Staphylococcus Aureus* resistant to methicillin among HCWsat Al-Ahrar Teaching Hospital.

Methods: A cross-sectional study was focusedon 163 HCWs. Nasal swabs were collected for detection of mupirocin and methicillin resistant isolates and their antimicrobial susceptibility pattern by standard bacteriological procedures. Then molecular detection of resistant genes by PCR was done.

Results: The whole nasal carriage of*Staphylococcus Aureus* resistant toMupirocin in our study was 1.2%. The prevalence of resistance tomupirocin amongMRSA isolates was 4.4%.

Conclusion: As the resistance rate to mupirocin was not high, so it can be used in nasal decolonization of MRSA among medical staff and patients.

Keywords:

Mupirocin, resistance, MRSA, antibiotics, Health Care Workers.

Introduction:

Staphylococcus aureus (*S.aureus*) is a one of commensal microflora in many body areas such as axillae, hands, rectum, perineum, gastrointestinal tract, vagina and skin. But the highest reservoir of *S. aureus* is the nares.*S.aureus* and MRSA are members of the most common hospital

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Received 05 March 2021; Accepted 01 April 2021.

acquired pathogens which not only cause increased mortality and morbidity rates but also increase the duration of hospital stay and cost. HCWs act as carriers, reservoirs, or victims of cross-transmission ofMRSA. Eradication of staphylococcal colonization is considered as an important strategy to prevent infection and transmission of these strains**.** [1]Mupirocin (MUP), pseudomonic acid or Bactroban is a derivative drug of crotonic acid which was extracted in 1971from Pseudomonas fluorescens. It was first presented in 1976 as a favorable remedy against Gram-positive bacteria. Since then, MUP has become available as an antimicrobial agent that hinderscreationof proteins through competitive inhibition of bacterial isoleucyl-tRNA synthetaseand is used to decolonize the anterior nares. However, the prolonged use of MUP has directed to itsresistance among isolates of*S. aureus***.** [2]Therefore, we aimed to evaluateMUP resistance in the nasal carriage of*Staphylococcus Aureus* resistant to methicillinbetween HCWs in an Egyptian Tertiary Care Hospital, so we can develop a better MRSA control and apolicy forinfection control by instituting the use of different options to prevent the colonization and spread of infection in case of resistance.

Subject and Method:

A Cross-sectional study was done at Al Ahrar Teaching Hospital, a tertiary care hospital, Zagazig, Sharkia governorate, Egypt. This study was done in the period from November 2018 to June 2019.

Subjects:

This study included 163HCWs (doctors, nurses, pharmacist, housekeeping, technician, and security guards) at Al Ahrar Teaching Hospital. Their demographic data (name, age, sex, residence, occupation) were collected.

Sample collection:

Samples were taken from both nostrils of HCWs by disposable sterile cotton swab after moistening it with sterile distilled water. The swabs were rubbed very well three times over the inner wall of ala nasi and nasal septum. The swabs were transmitted to the laboratory of the Department of Medical Microbiology and Immunology, Faculty of Medicine, Zagazig University within one hour to process it.

Sample processing:

We cultured the samples on Mannitol salt Agar (Oxoid, UK) , they were incubated for 48 hoursat 37°C. Mannitol-positive colonies were re-cultured on plates ofnutrient agar for 24 hours at 37°C. Isolated colonies were identified by Gram stain . *S.aureus* suspected Colonies were tested for catalase, coagulase and deoxyribonuclease (DNase) by typical microbiological procedures**.** [3]Catalase-positive, Coagulase-positive and DNase-positive Isolates were considered

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S.aureus.Antibiotic susceptibility test for all isolated strains were detected by standardized disk diffusion on Müeller Hinton Agar (Becton-Dickinson, Sparks, USA) by Kirby–Bauer disc diffusion technique**.**[4]The antibiotics used in this study included: Mup (20µg), Mup (5µg), cefoxitin (30µg), clindamycin (2 µg), ciprofloxacin (5 µg), penicillin (10 units), rifampin (5 µg). All of these discs are manufactured by BD BBL™sensi disc™, USAexcept Mup 20µg and Mup 5µg are manufactured by Oxoid, UK**.** Diameters of inhibition zones were measured with a ruler on the under surface of the Petri-dishes and dissected incope with thestandards of the Clinical Laboratory Standards Institute (CLSI) 2018.[5]Isolates having a zone diameter ≥ 22 mm against 30µg cefoxitin disc were considered susceptible to Methicillin, while those having a zone diameter ≤ 21 mm against 30µg cefoxitin disc were considered Methicillin resistant. *S.aureus* isolates were considered sensitive to Mup 5 µg when having a zone diameter ≥14 mm, while isolates having a zone diameter <14 mm were considered resistant. *S.aureus* isolates were considered sensitive to mupirocin 20 µg when having a zone diameter ≥17 mm. Isolates of*S.aureus* with a zone diameter 6-16 mm were deemed as low-level resistant, while those with no inhibition zone were deemed as high-level resistant**.** [6.7]

Molecular detection:

Multiplex PCR Assay was used for MRSA and MUPRSA isolates to identify *S.aureus* gene (nuc), methicillin resistant gene (mecA) and mupirocin resistant gene (MupA and Mup B) as following: Extraction was done using Thermo Scientific Gene JET Genomic DNA Purification Kit, from USA, according to manufacturer's instructions**.** We used Platinum™ SuperFi II PCR Master Mix(Invitrogen, Thermo Fisher Scientific, USA) for amplification which was done according to manufacturer's instructions. Primers used are shown in table (1).[8] The amplification reaction was done in a 0.2mL, thin-walled, nuclease-free PCR tube on ice. The total 50 µlvolume PCR mix was formed from 5 µl template DNA, 25 µl 2X Platinum™ SuperFi™ II PCR Master Mix, 0.2 µM of each forward and reverse primer, and autoclaved distilled water to the rest of volume. . The reaction was placed in the pre-heated thermal cycler with amplification conditions were as following: the initial denaturation was achieved by one cycle of 98°C for 1 min. DNA amplification was achieved by: 40cycles each lastsfor 10 sec at 98°C, for 30 sec at57°C and for 1min at 72°C. The final extension consists of one cycle at 72 °C for 5 min. The products of amplified PCR were visualized by electrophoresis by 2 % agarose gel**.** [9] The band of Nuc gene was at 279 bp, the band of MecA gene was at 112bp, The band of MupA gene was at 456 bp and the band of Mup B gene was at 674bp (Table1).

Table 1: Used Primers in multiplex PCR

Primer	Sequence	Relevant product size
Nuc	**F-GCGATTGATGGTGATACGGTT** **R- AGCCAAGCCTTGACGAACTAAAGC**	**279bp**
MecA	**F-GTGAAGATATACCAAGTGATT**	**112bp**

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	R-ATCAGTATTTCACCTTGTCCG	
MupA	**F-TATATTATGCGATGGAAGGTTGG** **R- AATAAAATCAGCTGGAAAGTGTTG**	**456bp**
MupB	**F-CTAGAAGTCGATTTTGGAGTAG** **R-AGTGTCTAAAATGATAAGACGATC**	**674bp**

Statistical analysis:

The Statistical Package for Social Science (SPSS) version 11.0 (IBM, USA)was used for performing the statistical analyses.For quantitative variables:data were stated as means ± standard deviation and range. For categorical data:data were stated as number and percentage. Independent t-test was for comparing means of two independent samples of normally distributed data whileChi-square test (X^2) was used to assess the relation among the qualitative data.*P*-values of <0.05 were supposed significant.

Results:

The prevalence of MRSA was (45/163) 27.6% from all isolates while the prevalence of MRSA isolates in *S.aureus* isolates was (45/48) 93.8%. The prevalence of Mup resistance was (2/163) 1.2% from all isolates. The prevalence of Mup resistance in MRSA isolate was (2/45) 4.4%. For antibiotic susceptibility testing, the Mup RSA isolates among MRSA strains (2) have higher sensitivity to ciprofloxacin (100%), while Mup SSA isolates among MRSA strains (43) show higher sensitivity to MUP (100%), rifampicin (100%) and clindamycin (90.7%) (Table2).There is a considerable relation between presence of MUP resistant isolates and working in ICU (*p-value equals 0.02*) (Table 3).The detection of PCR product was done by using gel electrophoresis, and only one sample shows 3 bands (photo1).Regarding risk factors of MUP resistant isolates in MRSA isolates, history of prior pseudomonas infection (within 1 year) and prior cefepime use (within 1 year) increased significantly the risk of MUP resistant MRSA isolates by 87 folds (*P*-value= 0.015) while prior exposure to mupirocin (1 year) did not increase that risk.By discdiffusion method, two MRSA isolates were mupirocin resistant, one of them showed high-level resistant and the other showed low-level resistant. By PCR only high level mupirocin resistant strain showed MupA gene .Using disc concentration (Mup 5 µg, Mup 20µg, and both Mup 5 µg& Mup 20µg) showed the same sensitivity 95.6%, specificity 93.8%, same positive predictive value 93.5% and same negative predictive value 95.7% with the same accuracy 94.6% in prediction of mupirocin resistance**.**

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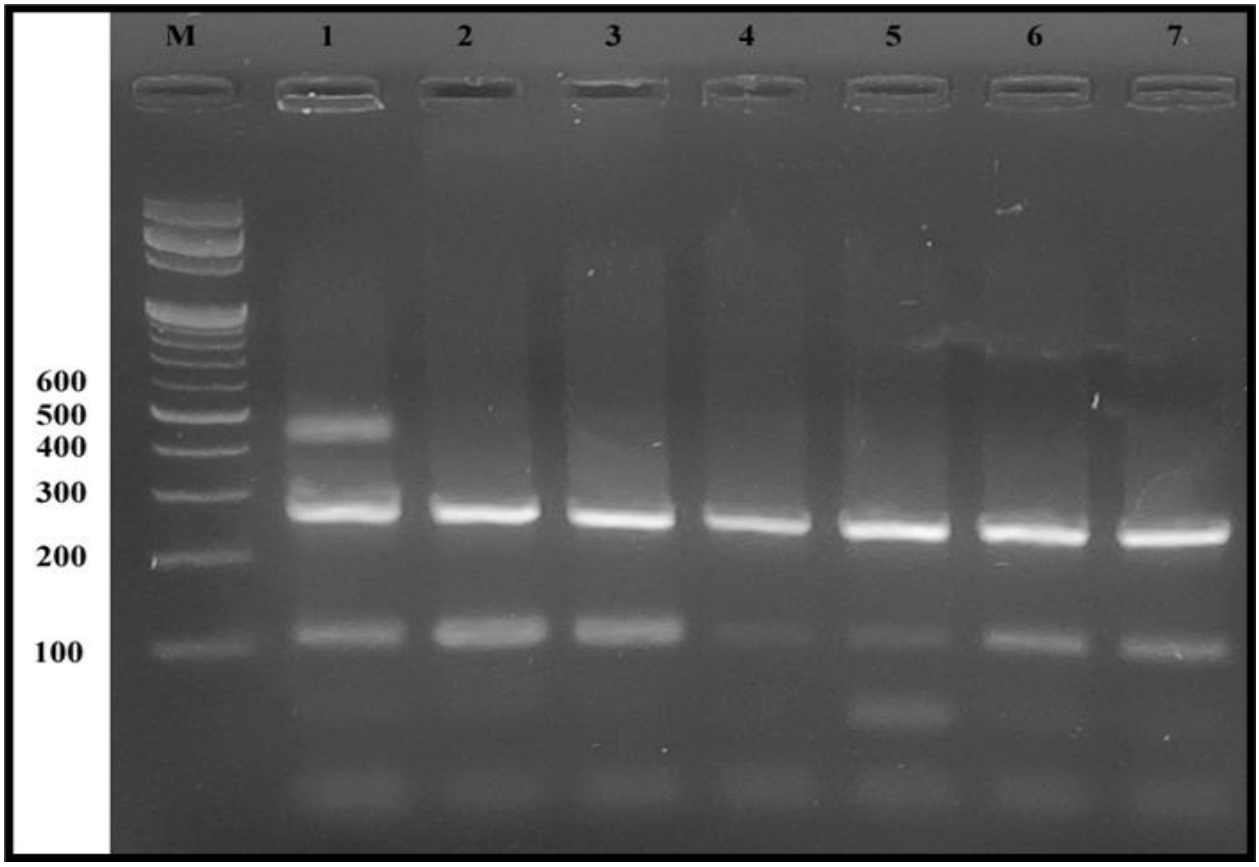

Photo1: The detection of PCR product by gel electrophoresis shows the 279 bp band for nuc, the 112 bp band for mecA and the 456 bp band for mupA. Only sample in lane 1 showed the 3 bands specific for mecA, nuc and mupA genes.

Table 2: Antibiotic susceptibility pattern of Mup RSA isolates among MRSA strains:

Variable	MupRSA †(N*=2)				MupSSA ‡ (N*=43)			
Antibiotic conc (ug\ml)	Sensitive		Resistant		Sensitive		Resistant	
	N*	%	N*	%	N*	%	N*	%
Cefoxitin 30	0	0	2	100	3	7	40	93
Clindamycin 2	0	0	2	100	39	90.7	4	9.3
Rifampicin 5	1	50	1	50	43	100	0	0
Ciprofloxacin 5	2	100	0	0	33	76.7	10	23.3
Penicillin 10 u	0	0	2	100	1	2.3	42	97.7
Mupirocin 20	0	0	0	0	43	100	0	0
Mupirocin 5	0	0	2	100	43	100	0	0

N: number, †MupRSA: mupirocin resistant *S.aureus*, ‡Mup SSA: mupirocin sensitive *S.aureus

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Table 3: Nasal carriage of Mup RSA and Mup SSA among MRSA (n=45) isolates:

Variable	MupRSA†		MupSSA ‡		P-Value	Odds Ratio (95% Confidence Interval)
	N=2	%	N=43	%		
Age in years						
<30	**0**	**0**	**18**	**41.8**	**0.468**	**1.87(0.11-32.1)**
30–40	**1**	**50**	**15**	**34.9**		**3.3 (0.19-57.67)**
>40	**1**	**50**	**10**	**23.3**		
Sex						
Female	**2**	**100**	**35**	**81.4**	**1**	**1.2 (0.05-27.31)**
Male	**0**	**0**	**8**	**18.6**		
Years of working						
0–9	**0**	**0**	**25**	**58.1**	**0.214**	**2.59(0.15 – 44.7)**
9–15	**1**	**50**	**12**	**27.9**		**6.17 (0.3 – 112.41)**
15–29	**1**	**50**	**6**	**14**		
Occupation						
Doctors	**0**	**0**	**6**	**14**	**1**	**1.15 (0.05-26.89)**
pharmacists	**0**	**0**	**1**	**2.3**	**1**	**5.67 (0.18 – 177.69)**
Nurses	**1**	**50**	**24**	**55.8**	**1**	**0.79 (0.05 – 13.5)**
House keeping	**1**	**50**	**9**	**20.9**	**0.399**	**3.78 (0.21 – 66.47)**

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Technicians	**0**	**0**	**2**	**4.7**	**1**	**3.32 (0.12 – 89.46)**
Security guards	**0**	**0**	**1**	**2.3**	**1**	**5.67 (0.18 – 177.69)**
Department						
Intensive care unit						
Pediatric	**2**	**100**	**5**	**11.6**	**0.02***	**3.32(1.48 – 829.22)**
Gastro intestinal tract	**0**	**0**	**7**	**16.2**	**1**	**0.97 (0.04 - 22.48)**
Gynaecology	**0**	**0**	**3**	**7**	**1**	**2.31 (0.09 – 58.32)**
Surgery	**0**	**0**	**5**	**11.6**	**1**	**0 (0 – 29.77)**
Laboratory	**0**	**0**	**8**	**18.6**	**1**	**0.84 (0.04 – 19.06)**
Out patients clinics	**0**	**0**	**3**	**7**	**1**	**2.31 (0.09 – 58.32)**
Neurology	**0**	**0**	**6**	**14**	**1**	**1.15 (0.05-26.89)**
Nephrology	**0**	**0**	**3**	**7**	**1**	**2.31 (0.09 – 58.32)**
	0	**0**	**3**	**7**	**1**	**2.31 (0.09 – 58.32)**

†MupRSA: mupirocin resistant *S.aureus,* ‡Mup SSA: mupirocin sensitive *S.aureus*

Discussion:

MRSA has been considered as one of the prevalent causes of nosocomial infections, that it is resistant to various classes of antibiotics**.** [10]The magnitude of the problem in Egypt is massive with estimates of more than 75% of Health care associated *Staph. aureus* infections to be MRSA strains. [11]Mup is a topical antibiotic which intervenes with bacterial protein synthesis that can be used for suppression of staphylococcal nasal colonization and control of MRSA transmission in Health Care setting**.** The increase in non-rationalized use of antibiotics may result in the expansion of MupRSA, leaving the clinicians with few choices to prevent the MRSAspread .[12]In the current study, the prevalence of Mup resistance among all our nasal isolates was 1.2% (2/163); one was ahigh level of resistance and the other was a low level of resistance. This result was in consistence with the prevalence of Mup resistance reported byOthman. (2013) which was 2%(6/300). The six isolates were of high level resistance**.**[12]Gadepalli *et al.* found that the prevalence of Mup resistance in an Indian hospital was 6% (12/200); 10/200 were of HLR and 2/200 were of LLR.In this study, the low percentage of mupirocin resistance may be due to the lack of the use of Mup as a routine decolonize of *S. aureus* at Al- Ahrar Teaching Hospital and due to small sample size.[13]Inthis study,the Prevalence of Mup resistant isolates in MRSA isolate

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was 4.4%.In Egypt 2013, Othmanreported that the Prevalence of isolates resistant to Mup in MRSA isolate was 3.7%. [12] On the other hand, in a study done byJones *et al***.** revealed a high rate of mup resistance was 13.2% among MRSA isolates.[14] While in Spain, Perez-Roth *et al.*, showed that around 12% of MRSA isolates possessed Mup resistance. In the current study, Mup RSA among MRSA isolates were 2 isolates, while Mup SSA among MRSA cases were 43. Mup RSA was resistant to cefoxitin, clindamycin and penicillin by (100%) as well, while it was sensitive to rifampicin (50%) and ciprofloxacin (100%). [15] Another study were done by Simor *et al*.where Mup RSA isolates showed, 85% resistant to clindamycin, 4% resistant toRifampicin and 75% resistant tociprofloxacin.[16] MupSSA isolates in our study, showed 100% sensitivity to rifampicin in addition to Mup. Similar results reported by a previous study. [16]In the current study, there was a significant relation between the presence of Mup resistant isolates and working in ICU (*P*- value =0.02). There was non-significant relation between nasal carriage of Mup resistant MRSA isolates and either age, gender, years of working, occupation or department of the studied patients other than ICU. These findings disagreed with a previous study where theyfound no effect of working in ICU and Mup resistance asall HCWS in the study were sensitive to Mup in spite of working in ICU**.**[17] In current study, history of prior *Pseudomonas* infection (within 1 year) and prior cefepime use (within 1 year) increased significantly risk of mupirocin resistant MRSA isolates by 87 folds. These results are almost in agreement with another study where they reported that MRSA isolates from infected patients with *Pseudomonasaeruginosa* in the year before the cultures were 4.85 times prospective to show Mup resistance compared to cultures from patients with no history of this infection and previous use of cefepime to be a liberated predictor of Mup resistance.[18]The association between *Pseudomonas* infection and Mup resistance is attributed to Mupirocin which is produced by *Pseudomonas fluorescens*bacterium. Also, *Pseudomonas* is insensitive to Mup resulting from its innate resistance to its produced antibiotic. [19]We found that Mup resistance was not related toprior exposure to Mup . In contrast, other studiesidentified that long, extensive or unplanned use and various courses of Mup are all relatedto the increase of Mup resistance. [16, 20] By disc diffusion method, we isolated only two isolates with Mup resistance. One of them revealed high level of resistance and the other revealed low level of resistance. This result is in consistence with a study done byKaur &Narayanwho reported that two isolates resistant to Mup among 20 MRSA isolates using disc diffusion method, one was high-level resistance and the other was low-level Mup resistance. [21] on the other hand, Boncompain *et al*.reported all MRSA cases were susceptible to Mup by disc diffusion method.[22]Low level of Mup resistancecomes from point mutations inside the host *ileS* gene and is of controversial clinical significance, while a high level of Mupresistance results from gaining of a transferable plasmid enclosing the MupA (or *ileS-2*) gene, encoding an additional isoleucyl-tRNA synthetase that is not Mup bound. [23, 24]Using disc concentration of Mup 5 µg and Mup 20 µg predict presence of mupirocin resistant with sensitivity 95.6%, specificity 93.8%, 93.5% positive predictive value and 95.7% negative predictive value with accuracy 94.6%. These findings were in agreement with previous studies.[6, 12]Nuc and Mec A genes were present in all

our isolates, but MupA gene was found only in one isolate. The Mup B gene was not found in any of our isolates. Similar findingswere detected by other studies. [8, 25]

Conclusion and recommendations:

The current study concluded that the rate of resistance to Mup was low at Al Ahrar Hospital, so Mupointment is still reliable to be used in MRSA nasal decolonization for HCWs.

Acknowledgments:
Authors present their sincere appreciation of all participants in the study.

Ethics declarations

Approval of Ethics and consent to participate

The study was agreed by Institutional Review Board (IRB) Committee of Zagazig Faculty of Medicine (approval no. Zu-IRB # 4422/1-4-2018). An informed consent form was signed by each participant.

Publication Consent

This research was consented for publication by all the authors and respondents in this paper and it will be available on the internet.

Authors' contributions:

AA: designing draft, data collectingand analysing thisdata and paper writing.ME: data collecting and paper writing. AF: data collecting, paper revising. LA: designingdraft, data collecting, analysing thisdata andpaper writing. All authors have critically reviewed, approved the final draft and are responsible for the content and similarity index of the manuscript.

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