ORIGINAL ARTICLE

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* AND ITS ANTIBIOTIC SENSITIVITY PATTERN IN PATIENTS WITH VESICULOBULLOUS DISORDERS

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Background: Vesiculobullous disorders are among the leading causes of admission to dermatology. These are characterized by distinct mucocutaneous involvement and by the development of vesicles and bullae (i.e. blisters). Methicillin-resistant *Staphylococcus aureus* (MRSA) is a group of gram-positive bacteria distinct from other strains of Staph aureus. As the susceptibility of bacteria to antibiotics varies from region to region and from time to time, this study will determine the pattern of antimicrobial susceptibility of MRSA isolates to the commonly prescribed antibiotics in our population. The objective is to determine the frequency of methicillin-resistant Staphylococcus aureus and its antibiotic sensitivity pattern in patients with vesiculobullous disorders admitted to the Dermatology unit of Lady Reading Hospital (LRH), Peshawar. It was Cross-sectional and carried out in study Department of Dermatology, Lady Reading Hospital, Peshawar from Oct 23, 2020, to Apr 22, 2021. **Methods:** This study was carried out over 132 patients. After consent, Swabs of pus from the Vesiculobullous disorders were taken from all the patients and sent to a laboratory for culture. Staphylococcus aureus (MRSA) was labelled as Staphylococcus aureus bacteria by Kirby–Bauer disc diffusion method using oxacillin (1 µ gm.) disc on Mueller–Hinton agar (HiMedia Labs, Mumbai) with 24 hours incubation at 35 °C. **Results:** In this study, 132 patients were observed. The average age was 44.44 years ±13.74 SD. Male to female ratio was 1.30:1. There were 44(33.33%) patients who showed Methicillin Resistant Staphylococcus aureus (MRSA) in vesiculobullous disorders patients. **Conclusion**: In our population, the frequency of staphylococcus aureus bacteria in vesiculobullous disorders is high so it will be considered while treating such patients.

Keywords: Frequency; Staphylococcus aureus; Vesiculobullous disorders

Citation: Raziq HU, Ghafoorullah, Ali F, Ziaulhaq M, Ali R. Methicillin-resistant *Staphylococcus aureus* and its antibiotic sensitivity pattern in patients with vesiculobullous disorders. J Ayub Med Coll Abbottabad 2023;35(4):588–92.

DOI: 10.55519/JAMC-04-11896

INTRODUCTION

Methicillin resistant Staphylococcus aureus (MRSA) is a group of gram-positive bacteria that is distinct from other strains of Staph aureus.[1] MRSA has genotypically and phenotypically different strains[2], one that is predominant in hospitals known as hospital-acquired MRSA (HA-MRSA) and another less common that is community acquired Staphylococcus aureus (CA-MRSA)[2]. MRSA infection is one of the leading causes of hospital-acquired infections and is commonly associated with significant morbidity, mortality, duration of stay and treatment cost.

Vesiculobullous disorders are among the leading causes of admission to dermatology. These are characterized by distinct mucocutaneous involvement and by the development of vesicles and bullae (i.e., blisters).[3] Both vesicles and bullae are fluid-filled lesions and they are distinguished by size (vesicles are less than 1 cm while bullae are more than 1 cm). When these lesions rupture, they leave erosions. Several disorders belong to the spectrum of vesiculobullous disorders, e.g., immunobullous disorders (like pemphigus and pemphigoid)[4], inherited disorders (Epidermolysis Bullosa), drug induced (SJS, TEN). In these disorders, the skin barrier is not intact. Most of these disorders follow a relapsing and remitting course requiring prolonged antibiotic and immunosuppressive therapy which predisposes the patients to MRSA infection.[5]

Studies have shown that among the dermatological diseases, vesiculobullous disorders are the most common to be colonized by MRSA. In one study published in 2014, it was noted that the overall prevalence of MRSA in dermatology inpatients was 22.2%. Amongst all patients, the highest proportion of MRSA was in vesiculobullous disorders, i.e., 36.1% followed by eczema being the next most common disorder to be colonized by MRSA.[6] In another study conducted on MRSA in vesiculobullous disorders, the prevalence of MRSA was found quite high (32.6%).[7]

As vesiculobullous diseases are associated with significant morbidity and mortality and also, they are especially prone to MRSA, special care is essential for these patients, to prevent MRSA infection. In such patients, it is often the skin erosions that are colonized by MRSA which can enter the blood stream to cause pneumonia and septicemia, contributing significantly to the mortality of the patient.[8] Immunosuppressive therapy and comorbidities such as DM contribute to MRSA colonization in vesicubullous disorders.

A study published in 2014 showed that 36.1 % of all patients with vesiculobullous disorders had MRSA.[6] The sensitivity shows that 85% ciprofloxacin, 21.4% Clindamycin,44.4 gentamicin, 22.2% erythromycin, 10.7% penicillin, 100% vancomycin[9], 81.4% Chloramphenicol, 81.5% Amoxicillin, 97.6% Doxycycline were sensitive to MRSA.[10]

The frequency of MRSA in vesiculobullous diseases depends on a number of factors, i.e., patient demographics, comorbid conditions, medication use, intact skin barrier, nutritional status, number of hospitalizations and the services provided by health care system. There is a great variability seen amongst these factors. Also, the sensitivity of antibiotics against MRSA has evolved significantly in recent times. As susceptibility of bacteria to antibiotics varies from region to region and time to time, so this study will determine the pattern of antimicrobial susceptibility of MRSA isolates to the commonly prescribed antibiotics in our population. Findings of the study will help devise an appropriate hospital antibiotic stewardship policy to reduce the chances of MRSA-associated infections in this area.

Objectives are to determine the frequency of methicillin resistant Staphylococcus aureus and its antibiotic sensitivity pattern in patients with vesiculobullous disorders admitted to the Dermatology unit of Lady Reading Hospital (LRH), Peshawar.

Vesiculobullous disorders were diagnosed clinically by seeing vesicles, bullae and erosions of any size over the body and/or in oral cavity.

It was detected by Gram staining, culture and susceptibility testing after taking a sterile swab from erosions/bullae. Test for methicillin resistance were performed by Kirby–Bauer disc diffusion method using oxacillin (1µgm) disc on Mueller–Hinton agar (HiMedia Labs, Mumbai) with 24 hours incubation at 35 °C. Results were interpreted according to the criteria of CLSI.[11]

Antibiotic sensitivity testing was performed by Kirby–Bauer disc diffusion method for the following antibiotics: amikacin, ciprofloxacin, chloramphenicol, clindamycin, gentamicin, erythromycin, netilmicin, penicillin, rifampicin and vancomycin. Results were interpreted according to the criteria of CLSI.[9] The minimum inhibitory concentration (MIC) and zone inhibition diameters.

MATERIAL AND METHODS

After approval from the research and ethical review committee for this cross-sectional descriptive study, 132 patients who were admitted to the Dermatology Unit, Lady Reading Hospital Peshawar from Oct 23, 2020 to Apr 22, 2021, were diagnosed as vesiculobullous disorders based on history and clinical examination, fulfilling the inclusion criteria were inducted in the study. Demographic data like age, sex, address, were obtained from all patients diagnosed with vesiculobullous disorders admitted in the dermatology unit, LRH. Informed consent was taken from the patient or his/her next kin. A detailed history was taken from the patient and a complete physical examination was performed. A swab of a representative skin lesion were taken as per protocol by an expert dermatologist having FCPS with a minimum of three years post fellowship experience and was sent to laboratory for Gram staining, culture, and antibiotic susceptibility. All investigations were done in the laboratory of LRH and the frequency of MRSA was calculated among the total cases of patients with vesiculobullous disorders included in the study and antibiotic sensitivity pattern of MRSA were recorded.

Patients with primary bacterial infections before vesiculobullous disorder (e.g. Impetigo, folliculitis, furunculosis) and patients already labelled as MRSA were excluded. The data were recorded into a proforma and analyzed in SPSS version 20.0.

RESULTS

A total of 132 patients either gender admitted with vesicobullous disorders were included in the study. There were 79 (59.85%) males and 53 (40.15%) females. Male to female ratio was 1.30:1.

Average age of the patients was 44.44 years+13.74SD with range 14-80 years. Patient's age was divided in three categories, out of which most common age group for vesicobullous disorders was 41-60 years of age. There were 54 (40.9%) patients were of the age less than or equal to 40 years. 61 (46.2%) patients were in the age range of 41-60 years and 17 (12.9%) presented at more than 60 years of age. Average duration of vesicobullous disorders was 4.37years+2.6SD. Out of 132 vesicobullous disorders, there were 44 (33.33%) patients shows Methicillin Resistant Staphylococcus aureus (MRSA) in vesiculobullous

disorders while 88 (66.67%) patients have no MRSA. While antibiotic sensitivity shows that Chloramphenicol followed by gentamicin were more sensitive to the MRSA. (Table 1) Age wise distribution of MRSA shows that MRSA in older age were high as that of younger age. The patients having age less than or equal to 40 years of age have 25.9% MRSA while 74.1% patients have no MRSA, age group 41-60 years contain 37.7% MRSA and 62.3% shows no MRSA and patients having more than 60 years of age have 41.2% MRSA and 58.8% shows no MRSA, (Table 2). Gender wise distribution of MRSA shows that gender has shown role over MRSA. There were 41.8% patients having MRSA in male and 20.8% shows in female patients. While antibiotic sensitivity also shows significance except Amoxicillin, Ciprofloxacin and Vancomycin. Duration of disease shows that patients having more than one year of disease have greater proportion of MRSA than patients having less or equal to one year although statistically its was insignificant. Previous history of antibiotics also shows insignificant difference over MRSA in patients with vesiculobullous disorders.

Table-1: Methicillin resistant staphylococcus aureus and its antibiotic sensitivity in vesiculobullous disorders

		Count	%
MRSA	Yes	44	33.3
	No	88	66.7
Amoxicillin	S	19	14.4
	R	113	85.6
Ciprofloxacin	S	11	8.3
	R	121	91.7
Chloramphenicol	S	39	29.5
	R	93	70.5
Clindamycin	S	33	25.0
	R	99	75.0
Gentamicin	S	38	28.8
	R	94	71.2
Erythromycin	S	16	12.1
	R	116	87.9
Doxycycline	S	41	31.1
	R	91	68.9
Penicillin	S	16	12.1
	R	116	87.9
Rifampicin	S	31	23.5
	R	101	76.5
Vancomycin	S	34	25.8
	R	98	74.2

Table 2 Age wise distribution of methicillin resistant staphylococcus aureus and its antibiotic sensitivity among patients with vesiculobullous disorders

		Age (in years)						*p*-value
		<= 40.00		41.00 - 60.00		61.00+		
		Count	%	Count	%	Count	%	
MRSA	Yes	14	25.9%	23	37.7%	7	41.2%	0.312
	No	40	74.1%	38	62.3%	10	58.8%	
Amoxicillin	S	9	16.7%	5	8.2%	5	29.4%	0.073
	R	45	83.3%	56	91.8%	12	70.6%	
Ciprofloxacin	S	6	11.1%	4	6.6%	1	5.9%	0.628
	R	48	88.9%	57	93.4%	16	94.1%	
Chloramphenicol	S	13	24.1%	20	32.8%	6	35.3%	0.508
	R	41	75.9%	41	67.2%	11	64.7%	
Clindamycin	S	11	20.4%	16	26.2%	6	35.3%	0.443
	R	43	79.6%	45	73.8%	11	64.7%	
Gentamicin	S	14	25.9%	19	31.1%	5	29.4%	0.825
	R	40	74.1%	42	68.9%	12	70.6%	
Erythromycin	S	8	14.8%	7	11.5%	1	5.9%	0.603
	R	46	85.2%	54	88.5%	16	94.1%	
Doxycycline	S	14	25.9%	20	32.8%	7	41.2%	0.458
	R	40	74.1%	41	67.2%	10	58.8%	
Penicillin	S	8	14.8%	7	11.5%	1	5.9%	0.603
	R	46	85.2%	54	88.5%	16	94.1%	
Rifampicin	S	9	16.7%	15	24.6%	7	41.2%	0.111
	R	45	83.3%	46	75.4%	10	58.8%	
Vancomycin	S	10	18.5%	17	27.9%	7	41.2%	0.154
	R	44	81.5%	44	72.1%	10	58.8%	

DISCUSSION

Vesiculobullous disorders in dermatology patients are a cause of great concern. When lesions rupture, they leave behind a large area of erosion that forms a nidus of bacterial colonization; often, these bacteria cause severe infection, including septicaemia, and result in death.[6] Moreover, autoimmune bullous disorders usually require a prolonged hospital stay and powerful immunosuppressive drugs, which contributes to bacterial infection, especially MRSA.[11]

Sepsis in dermatology inpatients is a dreaded complication, especially in patients with pemphigus and toxic epidermal necrolysis (TEN) and contributes significantly to mortality.[12]

The prevalence of MRSA all over the world is increasing. MRSA infection is high among dermatology in-patients with a prevalence rate of about 22.2%; vesiculobullous disorders (e.g: PV) were the most common disorders infected.[6] Aghmiyuni *et al*.[13] showed that Panton–Valentine Leukocidin gene carried by MRSA was high in PV patients. In addition, Kiran *et al*.[14] reported that 40.81% of the studied PV patients were colonized by S. aureus; 30% of them were MRSA. Areas such as the nostrils, axillae, perineum, and web spaces are the sites frequently showing MRSA colonization. Special care is essential for PV patients to prevent MRSA infection.[6]

The age of patients in this study ranged from 14 to 80 years; most patients were in the 4-6th decade, a pattern seen in studies worldwide.[11] In a study by Kanwar and De, however, most cases were aged 20 to 40 years.[15]

There was a male preponderance in this study with a male/female ratio of 1.30:1. The male preponderance in this study could be due to the fact that the majority of the cases in this study were manual and skilled workers who are more prone to trauma, as well as the risk of close physical contact amongst themselves. The role of close physical contact in MRSA acquisition has been presented in previous studies.[16] Male preponderance has been found in other Indian studies also.[17,18] However, in the study by Asati *et al*., there was a female preponderance.

Studies have shown that the duration of illness in vesiculobullous disorder is directly associated with MRSA infection. However, in our study with MRSA detected in 44 patients, most patients had a duration of illness less than 1 year (statistically insignificant [*P*>.05]), a finding similar to Shafi *et al*.[20]

Methicillin-resistant *S aureus* in this study was isolated most often from blisters and erosions. Vesiculobullous disorders and drug reactions (e.g: Stevens-Johnson syndrome, TEN) are characterized by blisters that rupture to form erosions and crusting, which form fissures in the epidermal barrier function that are nidi for colonization by microbes, especially S.aureus and MRSA in particular; later, these bacteria can enter dermal vessels and then the bloodstream, leading to septicemia.[21]

The prevalence of MRSA in this study was 32.6% (14/43), which is high compared to other studies. Pemphigus vulgaris was the most common disorder infected by MRSA in this study (57.1% [8/14] of MRSA isolates),[6,18] a finding that reveals that the incidence of MRSA is high among staphylococcal isolates in vesiculobullous disorders. However, the high incidence of MRSA in this study could be a reflection of the number of patients with a severe and chronic vesiculobullous disorder, such as PV, and serious drug reactions such as TEN referred to our tertiary-care centre, where we get a large number of patients affected by autoimmune and drug-induced vesiculobullous disorders. Similar findings have been reported by Stryjewski *et al*.[22]

A high prevalence of MRSA in a dermatology unit has grave consequences, contributing to morbidity and mortality in particular among patients with a vesiculobullous disorder.

A total of 44 patients in the present study showed presence of gram-positive cocci arranged in clusters and SA were grown in culture in all these cases. Thus, the study showed high correlation between gram stain and pus culture and sensitivity for SA. SA was the most common organism isolated in this study accounting for 52 cases (85.5%). This was much higher compared to the studies by Asati *et al*., Sharma *et al*., and Malhotra *et al*., indicating a very high prevalence of SA among dermatology inpatients at our institute.[17–19]

The antibiotic sensitivity pattern of the present study indicated that all the MRSA strains were resistant to penicillin, cloxacillin, and erythromycin. All the MRSA strains were sensitive to vancomycin and Doxycycline while 93.2% were sensitive to clindamycin, and rifampicin. This is an interesting finding since clindamycin and rifampicin are cheaper and easily available antibiotics than vancomycin, and thus can be considered as first-line antibiotic for MRSA in resource poor situations or when the latter is not available.

Similar findings were echoed in the studies by Asati *et al*., Sharma *et al*., and Malhotra *et al*.,[17–19] However, in the study by Sharma *et al*., the sensitivity of MRSA to amikacin was only 41.2%.[17] In the study by Asati *et al*., MRSA was also sensitive to teicoplanin which was not tested in the present study.[19] The newer antibiotics which are effective against MRSA are Tigecycline, Ceftobiprole Medocaril, daptomycin and Uinupristin-dalfopristin, and the newer generation carbapenems.[23,25] Interestingly, studies have shown that MRSA and even vancomycin-resistant *Staphylococcus aureus* may be sensitive to the older generation antibiotics doxycycline and cotrimoxazole.[23,2]

This study highlights that prolonged duration of illness, prolonged antibiotic and steroid therapy, and DM were relative risk factors for acquiring MRSA. This study also highlights that MRSA infection is high among dermatology inpatients, especially those with vesiculobullous disorders, since in most situations they are admitted in the general wards, unlike their Western counterparts who are admitted in the burns ward and ICU units. Therefore, admitting our vesiculobullous patients in burns wards and ICU units warrants consideration. This study also highlights the fact that MRSA may respond to relatively cheaper antibiotics.

CONCLUSION

Today complications due to vesiculobullous disorders are not only the most prevalent, but are the most challenging

issue in this era of dermatology. In conclusion, our pilot study highlighted for the first time the bacterial ecology of vesiculobullous disorders in this part of the world, showing a high prevalence of MRSA strains. These features appear close to those previously described in other studies. This trend is alarming and could indicate a misuse of antibiotic agents and/or high prevalence of cross-transmission of microorganisms. Improving knowledge of the local ecology of vesiculobullous disorders in Pakistan looks to be important for a more rational empirical prescription of antibiotic agents in Pakistan if such results are confirmed by further studies in other Pakistani areas.

AUTHORS' CONTRIBUTION

RAZIQ: Conceptualization, data collection, data analysis and interpretation, literature search, write-up. GH: Data analysis, write-up, literature search, proof reading. FA: Data interpretation, write-up, literature search. MZ: Data collection, proof reading. RA: Concept, supervision, proof reading.

REFERENCES

1. Saeed K, Gould I, Esposito S, Ahmad-Saeed N, Ahmed S, Alp E, *et al*. Panton–Valentine leukocidin-positive Staphylococcus aureus: a position statement from the International Society of Chemotherapy. Int J Antimicrob Agents 2018;51(1):16–25.
2. Vysakh PR, Jeya M. A comparative analysis of community acquired and hospital acquired methicillin resistant Staphylococcus aureus. J Clin Diagn Res 2013;7(7):1339–42.
3. Anuradha J, Raghavendra R, Balbir SB. Advanced diagnostic techniques in autoimmune bullous diseases. Indian J Dermatol 2017;62(3):268–78.
4. Mohammadreza S, Mahmood F, Maryam T. Spectrum of autoimmune vesiculobullous diseases in Iran: a 13-year retrospective study. Clin Cosmet Investig Dermatol 2016;9:15–20.
5. Albers LN, Liu Y, Bo N, Swerlick RA, Feldman RJ. Developing biomarkers for predicting clinical relapse in pemphigus patients treated with rituximab. J Am Acad Dermatol 2017;77(6):1074–82.
6. Vijayamohan N, Nair SP. A study of the prevalence of methicillin-resistant Staphylococcus aureus in dermatology inpatients. Indian Dermatol Online J 2014;5(4):441–5.
7. Thomas MG, Nair SP. MRSA in Dermatology Inpatients with a Vesiculobullous Disorder. Cutis 2018;101(6):458–61.
8. Kayani M, Aslam A. Bullous pemphigoid and pemphigus vulgaris. BMJ 2017;357:j2169.
9. Wu M, Tong X, Liu S, Wang D, Wang L, Fan H. Prevalence of methicillin-resistant Staphylococcus aureus in healthy Chinese population: A system review and meta-analysis. PLoS One 2019;14(10):e0223599.
10. Dilnessa T, Bitew A. Prevalence and antimicrobial susceptibility pattern of methicillin resistant Staphylococcus aureus isolated from clinical samples at Yekatit 12 Hospital Medical College, Addis Ababa, Ethiopia. BMC Infect Dis 2016;16:398.
11. Lehman JS, Murell DF, Camilleri MJ. Infection and infection prevention in patients treated with immunosuppressive medications for autoimmune bullous disorders. Dermatol Clin 2011;29(4):591–8.
12. Nair PS, Moorthy PK, Yogiragan K. A study of mortality in dermatology. Indian J Dermatol Venereol Leprol 2005;71(1):23–5.
13. Aghmiyuni Z, Khorshidi A, Moniri R, Soori T, Musavi S. The prevalence of S. aureus skin and soft tissue infections in patients with pemphigus. Autoimmune Dis 2016;2016:7529078.
14. Kiran KC, Madhukara J, Abraham A, Muralidharan S. Cutaneous bacteriological profile in patients with pemphigus. Indian J Dermatol 2018;63:301–4.
15. Kanwar AJ, De D. Pemphigus in India. Indian J Dermatol Venereol Leprol 2011;77(4):439–49.
16. Begier EM, Frenette K, Barrett NL, Mshar P, Petit S, Boxrud DJ, *et al*. A high morbidity outbreak of methicillin resistant Staphylococcus aureus among players on a college football team, facilitated by cosmetic body shaving and turf burns. Clin Infect Dis 2004;39(10):1446–53.
17. Sharma VK, Asati DP, Khandpur S, Khilnani GC, Kapil A. A study of sepsis in dermatology ward: A preliminary report. Indian J Dermatol Venereol Leprol 2007;73(5):378–82.
18. Malhotra SK, Malhotra S, Dhaliwal GS, Thakur A. Bacteriological study of pyodermas in a tertiary care dermatological center. Indian J Dermatol 2012;57(5):358–61.
19. Asati DP, Sharma VK, Khandpur S, Khilnani GC, Kapil A. Clinical and bacteriological profile and outcome of sepsis in dermatology ward in tertiary care center in New Delhi. Indian J Dermatol Venereol Leprol 2011;77:141.
20. Shafi M, Khatri ML, Mashima M, Ben-Ghazeil M. Pemphigus: a clinical study of 109 cases from Tripoli, Libya. Indian J Dermatol Venereol Leprol 1994;60:140–3.
21. Miller LG, Quan C, Shay A, Mostafaie K, Bharadwa K, Tan N, *et al*. A prospective investigation of outcomes after hospital discharge for endemic, community-acquired methicillin-resistant Staphylococcus aureus skin infection. Clin Infect Dis 2007;44(4):483–92.
22. Stryjewski M, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant Staphylococcus aureus. Clin Infect Dis 2008;46(Suppl 5):S368–77.
23. Elston DM. Methicillin-sensitive and methicillin-resistant Staphylococcus aureus: Management principles and selection of antibiotic therapy. Dermatol Clin 2007;25(2):157–64.
24. Elston DM. Community-acquired methicillin resistant Staphylococcus aureus. J Am Acad Dermatol 2007;56(1):1–16.
25. Goyal R, Das S, Mathur M. Colonization of methicillin resistant Staphylococcus aureus among health care workers in a tertiary care hospital of Delhi. Indian J Med Sci 2002;56(7):321–4.

Submitted: March 17, 2023	*Revised: : October 7, 2023*	*Accepted: October 7, 2023*

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