THE AGA KHAN UNIVERSITY

eCommons@AKU

Department of Pathology and Laboratory Medicine

Medical College, Pakistan

11-2017

Susceptibility pattern of methicillin resistant staphylococcus aureus to vancomycin and other alternate agents: Report from a private sector hospital laboratory

Faryal Saleem
Aga Khan University

Naima Fasih
Armed Forces Hospital

Afia Zafar
Aga Khan University, afia.zafar@aku.edu

Follow this and additional works at: https://ecommons.aku.edu/pakistan_fhs_mc_pathol_microbiol

 Part of the Microbiology Commons, and the Pathology Commons

Recommended Citation

Saleem, F., Fasih, N., Zafar, A. (2017). Susceptibility pattern of methicillin resistant staphylococcus aureus to vancomycin and other alternate agents: Report from a private sector hospital laboratory. *Journal of Pakistan Medical Association, 67*(11), 1743-1746.
Available at: https://ecommons.aku.edu/pakistan_fhs_mc_pathol_microbiol/1178

SHORT REPORT

Susceptibility pattern of methicillin resistant Staphylococcus aureus to vancomycin and other alternate agents: report from a private sector hospital laboratory

Faryal Saleem,[1] Naima Fasih,[2] Afia Zafar[3]

Abstract

With increasing prevalence of methicillin resistant Staphylococcus aureus in clinical settings and injudicious use of antibiotics, resistance among MRSA against commonly used antibiotics is increasing. To assess the susceptibility pattern of MRSA against vancomycin, linezolid, tigecycline, rifampicin, fosfomycin fusidic acid, clindamycin, trimethoprim-sulfamethoxazole and teicoplanin, minimum inhibitory concentrations (MICs) for given antimicrobials were performed on 234 MRSA clinical isolates using automated VITEK 2 system. Vancomycin, linezolid, rifampicin, clindamycin, co-trimoxazole and teicoplanin susceptibilities were interpreted according to CLSI breakpoints, while tigecycline, fosfomycin and fusidic acid were interpreted according to BSAC breakpoints. All isolates were found susceptible to vancomycin, tigecycline, teicoplanin and linezolid. Non-susceptibility of the isolates for rifampicin, fusidic acid and fosfomycin was noted for 58(25%). Co-trimoxazole and clindamycin were found less susceptible showing high resistance rates of 61.5% and 42.3%, respectively. Vancomycin resistance was not found, however an increased MIC of 1 μg/ml was observed in about 25% of clinical strains. Increase in vancomycin MICs in MRSA is of concern and alternative antimicrobial options must be evaluated and considered for treatment of MRSA infections. Continuous antimicrobial surveillance is needed to monitor resistance patterns and detect possible emergence of vancomycin non-susceptible isolates.

Keywords: MRSA, Staphyloccoccus aureus, minimum inhibitory concentration, MIC, vancomycin susceptibility

Introduction

Staphylococcus aureus is a significant healthcare threat in both community and hospital settings. Antimicrobial choices against S. aureus are getting limited as it continues to develop resistance to a range of antimicrobial agents. In the recent past, prevalence of methicillin resistant S. aureus (MRSA) strains has increased worldwide. According to available literature from Pakistan, its frequency of isolation from human infections ranges from 20-50%.[1,2]

Most of MRSA are also resistant to common anti-staphylococcal drugs such as aminoglycosides, fluoroquinolones, tetracycline, trimethoprim-sulfamethoxazole, macrolide-lincosamides.[3] For such strains, vancomycin is considered as a drug of choice, however high cost, toxicity and poor tissue penetration, especially in the lungs, bone and CNS remains an issue with its use. Additionally, emergence of vancomycin resistant and vancomycin intermediate S. aureus (VRSA & VISA) strains, in different parts of the world, including Pakistan is a matter of concern.[4] These issues have led to limited number of available therapeutic options against MRSA.

There is a need to explore alternative drugs that can be used to treat MRSA and probable VRSA infections in future. Antibiotics such as linezolid, tigecycline, rifampicin, fosfomycin and fusidic acid have been proved effective for MRSA infections internationally, but there is limited data regarding their efficacy in local clinical isolates. Therefore, this study aimed to assess the drug resistance against vancomycin, linezolid, tigecycline, rifampicin, fosfomycin, fusidic acid, clindamycin, trimethoprim-sulfamethoxazole and teicoplanin so as to guide for alternative therapeutic options to the physicians for the empirical as well as targeted use.

Methods and Results

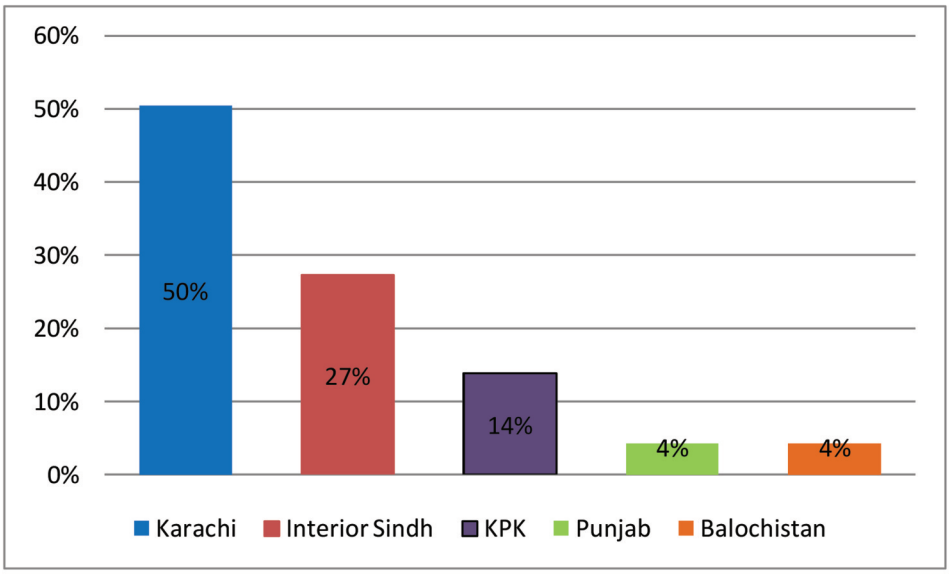
This cross sectional study was conducted at the clinical microbiology laboratory of Aga Khan University Hospital (AKUH). The AKUH is one of the largest tertiary care hospitals in Pakistan and its laboratory has a network of more than 200 collection units through which it caters inpatients as well as outpatients countrywide. Exemption for ethical approval was granted by Ethical Research Committee of the Aga Khan University (3209-Pat-ERC-14).

For this study, a total of 234 clinical isolates of S. aureus were included from period of May 2013 to April 2014. Duplicate

[1,3]Clinical Microbiology, Aga Khan University Hospital, Karachi, Pakistan, [2]Department of Pathology and Laboratory Medicine, Armed Forces Hospitals, Southern Region, Khamis Mushayt, KSA.
Correspondence: Afia Zafar. Email: afia.zafar@aku.edu

Table: Minimum Inhibitory Concentration of various antimicrobials for MRSA isolates (n =234) during the study period May 2013 to April 2014.

Antibiotic Tested	MIC breakpoint (ug/mL)			MIC range (ug/mL)	MIC50	MIC90	S (%)	I (%)	R (%)
	S	I	R						
Clindamycin	≤0.5	1-2	≥4	≤0.25 - ≥8	1.5	2	57.6	-	42.3
Vancomycin	≤2	4-8	≥16	≤0.5 - ≥2	1	1	100	-	-
Linezolid	≤4	N/A	≥8	≤0.5 - 4	2	2	100	-	-
Rifampicin	≤1	N/A	≥4	≤0.5 - ≥32	0.5	0.5	87.1	2.9	9.8
Co-trimoxazole	≤40	N/A	≥80	≤10 - ≥320	80	160	38.4	-	61.5
Teicoplanin	≤8	16	≥32	≤ 0.5 - 4	2	4	100	-	-
Tigecycline	≤0.5	N/A	≥0.5	≤0.12 - 0.5	0.25	0.5	100	-	-
Fosfomycin	≤32	N/A	≥32	≤8 - ≥128	64	64	79.4		20.5
Fusidic acid	≤1	N/A	≥1	≤0.5 - ≥32	8	16	77.3	19.6	2.9



MRSA: Methicillin-resistant Staphylococcus aureus

Figure: Geographic distribution of MRSA isolates.

samples from the same patient were excluded. All isolates were identified by colony morphology, gram staining, catalase, coagulase and DNase test. Methicillin resistance was detected by taking cefoxitin as a surrogate marker and was interpreted according to Clinical Laboratory Standard Institute (CLSI) breakpoints.[5] Cefoxitin was interpreted sensitive at (mimimum inhibitory concentration) MIC <4 µg/ml and resistant at MIC >8 µg/ml. Following the identification of MRSA, susceptibility testing was performed against vancomycin, linezolid, tigecycline, fosfomycin, rifampicin, fusidic acid, clindamycin, trimethoprim-sulfamethoxazole and teicoplanin was performed using automated VITEK 2 system (bioMe´rieux, France). Vancomycin, linezolid, rifampicin, clindamycin, trimethoprim sulfamethoxazole and teicoplanin were interpreted according to CLSI breakpoints.[5] Due to unavailability of clinical breakpoints for tigecycline, fosfomycin and fusidic acid in CLSI, susceptibilities were interpreted according to BSAC.[6]

The demographic and susceptibility data for study isolates was entered in Microsoft excel software. MIC50 and MIC90 were calculated for each tested antibiotic. Majority of the isolates were from pus (73.5%) and tissue (7.6%), followed by respiratory tract (7.6%) and blood (7.2%). In all 61% of isolates were from clinical samples of female patients while 39% were from male patients. Mean age of the patients was 35.5±21.54 years. Most of clinical specimens were from Karachi and interior Sindh (Figure). Overall, isolates showed varied susceptibilities to the tested antibiotics (Table). All isolates were susceptible to vancomycin, tigecycline, teicoplanin and linezolid. Non susceptibility of MRSA isolates for rifampicin, fusidic acid and fosfomycin was found to be less than 25%. Commonly used antimicrobials like co-trimoxazole and clindamycin were found less susceptible showing high resistance rates of 61.5% and 42.3% respectively. Fortunately, vancomycin resistance was not seen, however an increased MIC of 1 µg/ml was observed in about 25% (58/234) of clinical strains.

Discussion and Conclusion

In this study, though all isolates were found susceptible to vancomycin, its rising MIC is a cause of concern.

Increase in vancomycin MICs for MRSA is also reported from different parts of the world. In 2011, Kaleem et al.,[7] reported 46% of MRSA isolates to have an MIC of >1μg/ml. High vancomycin MICs have been associated with poor clinical outcomes, shown by Lodise et al.[8] in his study where 71% patients with MRSA bacteremia had vancomycin MICs of >1.5 μg/ml and these patients had a 2.4-fold increase in therapeutic failure compared to patients with MRSA isolates having vancomycin MICs of <1.0 μg/ml. Hidayat et al.[9] also found that despite achieving target trough concentration, patients with MRSA pneumonia and bacteraemia due to strains with higher MICs of >2 μg/ml had a poor treatment response.

In this study, we did not find resistance against linezolid, teicoplanin and tigecycline. These antibiotics are important especially in situations where its use is limited due to increased MICs, accessibility, bioavailability, toxicity or cost. Our findings in this regard are concordant with various studies published locally. Linezolid has been reported fully susceptible in MRSA isolates by Khalid et al. and Hannan et al.[10,11] Linezolid is cost effective and is available in oral and parenteral formulations which make it a viable option for the treatment of MRSA infections. Teicoplanin can also be used in a wide variety of gram positive infections such as septicaemia, endocarditis, skin and soft tissue infections. Moreover, its once daily dosing reassures good compliance during treatment of serious MRSA infections. Similarly, tigecycline is also an effective antibiotic for treatment of serious MRSA infections. However, use of these antibiotics must be conserved for serious cases only.

As per our findings, rifampicin, fosfomycin and fusidic acid have variable susceptibilities against MRSA isolates. Although proportion of fully resistant MRSA strains against fusidic acid is low, intermediate resistance of 19% strains to fusidic acid is alarming. Most probable reason for this development is the excessive use of this drug as skin ointment and its use as monotherapeutic agent. Although, rifampicin is a first line anti-tuberculous drug and is widely used in TB endemic area like Pakistan, its resistance remained low in study isolates. Comparable to our results, studies conducted by Bukhari et al. and Perveen et al showed 5% and 10% resistance to rifampicin, respectively.[12,13] Fosfomycin has a broad spectrum coverage ranging from MRSA, VRE and MDR gram negative rods. A review article evaluating the role of fosfomycin against MRSA isolates showed a susceptibility of approximately 80%, which makes fosfomycin a viable option for infections which are not responding to conventional therapy.[14] Unfortunately, around 61% isolates were found resistant to commonly used antimicrobials like co-trimoxazole and clindamycin therefore these antimicrobials cannot be used empirically until susceptibilities are confirmed. These antimicrobials are particularly useful in clinical scenarios where cost, bioavailability or accessibility of newer drugs is an issue.

A similar study was conducted in Lahore in 2013, where susceptibility of quinopristin/dalfoprisitin, linezolid and vancomycin for 50 MRSA isolates was evaluated.[15] In this study, all isolates showed 100% susceptibilities to above tested antimicrobials. However, their study had lower sample size and evaluated lesser number of antimicrobials. The strength of this study is the larger number of isolates and the use of Vitek 2 system to detect MICs. Limitation of this study is that a large proportion of samples are collected outside the hospital, so clinical data is not available in many cases due to which clinical outcomes could not be evaluated. Second limitation is that majority of specimens were from Karachi and interior Sindh, due to the presence of greater number of laboratory collection units in the given areas, so the data is not representative of entire country.

To conclude, vancomycin remains the drug of choice for the treatment of serious MRSA infections, however, emergence of clinical isolates with reduced susceptibility is worrisome. It is encouraging that current MRSA isolates are fully susceptible to linezolid, teicoplanin and tigecycline, and in situations where vancomycin is contraindicated one can use these drugs safely. Our findings also show that empirical use of erythromycin, clindamycin, co-trimoxazole and fusidic acid for treatment of MRSA infections should not be undertaken and prior antimicrobial susceptibilities are a must before initiating therapy with any of these options. Finally, our findings point towards the need of establishment of continuous drug surveillance mechanism to detect development of antimicrobial resistance against MRSA and possible emergence of VISA and VRSA strains in future.

Acknowledgement

We would like to thank Dr Kausar Jabeen for her technical input and Ms. Sobia Noshad for her assistance in data retrieval.

Disclaimer: The manuscript was presented at the 12th Conference on Infectious Diseases of the Medical Microbiology and Infectious Diseases Society of Pakistan held in Karachi, on March 7, 2015.

Conflict of Interest: None.

Source of Funding: None.

References

1. Malik N, Butt T, Arfan-ul-Bari. Frequency and antimicrobial susceptibility pattern of methicillin resistant Staphylococcus aureus. J Coll Physicians Surg Pak. 2009; 19:287-90.
2. Perwaiz S, Barakzi Q, Farooqi BJ, Khursheed N, Sabir N. Antimicrobial susceptibility pattern of clinical isolates of methicillin resistant Staphylococcus aureus. J Pak Med Assoc. 2007; 57:2-4.
3. Idrees F, Jabeen K, Khan MS, Zafar A. Antimicrobial resistance profile of Methicillin Resistant Staphylococcal Aureus from skin and soft tissue isolates. J Pak Med Assoc. 2009; 59:266-9.
4. MMWR. Recommendations and Reports: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, Epidemiology Program Office; 1997.
5. CLSI 2014 Clinical and Laboratory standard institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. 2012; 32: S20:30.
6. Howe RA, Andrews JM, BSAC Working Party on Susceptibility Testing. BSAC standardized disc susceptibility testing method (version 11). J Antimicrob Chemother. 2012; 67:2783-4.
7. Kaleem F, Usman J, Hassan A, Omair M, Khalid A, Uddin R. Sensitivity pattern of methicillin resistant Staphylococcus aureus isolatedfrom patients admitted in a tertiary care hospital of Pakistan. Iran J Microbiol. 2010; 2:143-6.
8. Lodise TP, Graves J, Evans A, Graffunder E, Helmecke M, Lomaestro BM, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant Staphylococcus aureus bacteremia treated with vancomycin. Antimicrob Agents Chemother. 2008; 52:3315-20.
9. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: efficacy and toxicity. Arch Intern Med. 2006; 166:2138-44.
10. Khalid A, Usman J, Faiz U, Kaleem F, Amir A, Omair M. In-vitro susceptibility of linezolid against methicillin resistant Staphylococcus aureus at a tertiary care hospital in Pakistan. J Microbiol Infect Dis. 2013; 3:203-6.
11. Hannan A, Absar M, Usman M, Naeem T, Saleem S, Arshad M. In vitro activity of linezolid against clinical isolates of methicillin resistant Staphylococcus. J Ayub Med Coll Abbottabad. 2009; 21:106-9.
12. Bukhari SZ, Ahmed S, Zia N. Antimicrobial susceptibility pattern of Staphylococcus aureus on clinical isolates and efficacy of laboratory tests to diagnose MRSA: a multi-centre study. J Ayub Med Coll Abbottabad. 2011; 23:139-42.
13. Perveen I, Majid A, Kanwal S, Naz I, Sehar S, Ahmed S, et al. Prevalence and antimicrobial susceptibility pattern of methicillin-resistant Staphylococcus aureus and coagulase-negative Staphylococci in Rawalpindi, Pakistan. Brit J Med Med Res. 2013; 3:198.
14. Falagas ME, Roussos N, Gkegkes ID, Rafailidis PI, Karageorgopoulos DE. Fosfomycin for the treatment of infections caused by Gram-positive cocci with advanced antimicrobial drug resistance: a review of microbiological, animal and clinical studies. Expert Opin Investig Drugs. 2009; 18:921-44.
15. Arshad F, Javed I, Mustafa T, Mushtaq S, Anwer S, Rafique F. Comparison of in vitro Efficacy of Quinopristin/Dalfopristin, Linezolid and Vancomycin for Methicil-lin Resistant Staphylococcus Aureus. Int J Pathlo. 2014; 12:8-15.