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Methicillin Resistant Staphylococcus Aureus (MRSA) Infections - Local Antibiogram Based Empirical Treatment Options

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Abstract:
Background*: The empirical treatment of patients with suspected Methicillin Resistant Staphylococcus aureus (MRSA) infections with newer anti-MRSA agents namely Vancomycin or Linezolid, need justification before prescribing. The first step for Staphylococcus aures infection is to begin with thorough source control namely removal of any device or draining pus collection. Then, second step is to evaluate patient risk profile for possible MRSA infection and third is select the anti-MRSA agent with more than 80% susceptibility from the local antibiogram data for MRSA clinical isolates for anti-MRSA agents.*
Materials and Methods*: This study is using retrospective antibiogram data for MRSA clinical isolates from tertiary care center at rural Karnataka for one year period from April 2021 to March 2022. WHONET 2020 software is used to make antibiogram. A total of 160 Staphylococcus aureus clinical isolates were included in the study. For Vancomycin, regional data was used.*
Results*: The overall prevalence of methicillin resistance during the study period was 36.25 per cent. Susceptibility of 80 percent or more was considered for recommending empirical therapy for a given antimicrobial. Doxycycline Linezolid, Teicoplanin and Nitrofurantoin showed more than 80% susceptibility compared to Gentamicin, Cotrimoxazole, Erythromycin and Clindamycin antimicrobials which showed less than 80% susceptibility among MRSA clinical isolates. National data for Vancomycin was 100% susceptible against MRSA clinical isolates. This data is used to make empirical treatment algorithm for suspected MRSA infections in patients.*
Conclusion: *Linezolid, Vancomycin are the workhorses for management of suspected MRSA infections. This usage could be reduced by opting the other anti-MRSA agent alternatives after the rigorous source control measures. The local susceptibility data for the newer anti-MRSA agents with minimum inhibitory concentrations could enhance options for serious MRSA infections. In this regard, laboratory strengthening with automation and adequate skilled manpower can address the gaps in data. The treating doctor must justify empirical anti-MRSA treatment for definite indications. The microbiologist must timely update prevalent local bugs and their antibiogram preferably with clear clinical indications to reduce inappropriate antimicrobial use.*
Key Word: *MRSA, antibiogram, WHONET*

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I. Introduction

Methicillin Resistant Staphylococcus aureus (MRSA) continues to be retained in the Bacterial Priority Pathogens List (BPPL) under high-priority pathogen category (WHO), due to its high estimated burden. (1) The availability of comprehensive global data helps to prioritize the bacterial pathogens to target the investments in R&D programmes, infection prevention and control (IPC) measures including stewardship programmes and surveillance. (2,3) For targeting MRSA, besides focusing on the compliance with hand hygiene measures and screening for carriage to control MRSA, care must be given to correct use of antibiotics. (4) As there are limited options to treat MRSA infections, the essential antimicrobial stewardship activity is to reduce empirical usage of anti-MRSA agents. This could be achieved through the periodic updates on the local surveillance data including MRSA prevalence and anti-MRSA treatment options from antibiogram preferably with syndromic approach. (5)

The MRSA prevalence has increased in both the community and the hospital settings.(6) In India, MRSA prevalence is varies between from 40% to 70% among S. aureus isolates, in both community and hospital settings (7). Each patient needs to be evaluated individually, firstly the probability of Staphylococcus aureus infection/suspicion; then do the MRSA risk assessment along with prompt source control measures. Methicillin Resistant Staphylococcus aureus (MRSA) is to be suspected if patient has the following risk factors (7–9) : recent hospital or skilled nursing facility admission/ residing in a community where there is a substantial incidence of

MRSA, chronic hemodialysis, recent antimicrobial therapy, indwelling lines/ devices, intravenous drug use, co-morbid disease (e.g., diabetes mellitus) or with prior history of MRSA infection.

The justification to start anti-MRSA agent for critical patient needs to be supported by local antibiogram preferably with syndromic approach. This is to reduce the off label inappropriate use of newer anti-MRSA antibacterials. If the local prevalence of MRSA is <10%, only empirical MSSA cover may be suggested till the culture reports indicate MRSA. (7) There are studies showing even the risk based empirical anti-MRSA therapy was not associated with reduced mortality for any group of patients hospitalized for pneumonia. These results question the value of empirical use of anti-MRSA therapy using existing risk approaches and reinstate the role of source control measures.(8) Anti-staphylococcal penicillins and cefazolin appear superior to vancomycin and other lipo/glycopeptides, if susceptible.(10) Further step in saving anti-MRSA antibacterials is to reduce even the third-generation cephalosporins and quinolones, which are implicated as a risk factor for increased MRSA / gram negative bacilli colonization and infection.(2)Here in this study, the local antibiogram data is integrated in to treatment flow chart for suspected MRSA infections in accordance with the guidelines. (3,5–7) The retrospective data is from tertiary care center at rural Karnataka for one year period from April 2021 to March 2022. A total of 160 Staphylococcus aureus isolates were included in the study. The overall prevalence of methicillin resistance during the study period was 36.25 per cent. Susceptibility of 80 percent or more was considered for recommending empirical therapy for a given antimicrobial. This is because, selection of antibiotics with resistance rates exceeding 10–20% is associated with an increased risk of treatment failure and selection of resistant strains. (11,12) At this healthcare facility, MRSA isolates showed more than 80% susceptibility for Teicoplanin, Linezolid and Doxycycline. For Nitrofurantoin both MRSA and MSSA showed more than 90% susceptibility. National (India) data for Vancomycin was 100% against MRSA isolates.(13,14)

II. Material And Methods

This retrospective descriptive study was carried out at Department of Microbiology, Dr. Chandramma Dayananda Sagar Institute of Medical Education & Research, India. The study period was from April 2021 to March 2022. All Staphylococcus aureus clinical isolates obtained during the one-year study period were included in the study. Data of the antimicrobial susceptibility pattern among Staphylococcus aureus was studied for ICU, wards and OPD location and specimen type.

Study Design: Retrospective descriptive study

Study Location: Dr. Chandramma Dayananda Sagar Institute of Medical Education & Research, Bengaluru, India

Study Duration: April 2021 to March 2022.

Sample size: Not applicable

Sample size calculation: Not applicable

Subjects & selection method: All cultures positive for Staphylococcus aureus.

Inclusion criteria: All cultures positive for Staphylococcus aureus

Exclusion criteria: None.

Procedure methodology

The data is from clinical laboratory, where Kirby Bauer disk diffusion testing for Cefoxitin was used to detect MRSA. This was recommended by CLSI (2021-22 edition) for detection of methicillin resistance. Staphylococcus aureus suspension equivalent to 0.5 Mc Farland standard was prepared for all isolates & tested with cefoxitin (30µg) disc, using Muller Hinton agar. All plates were incubated at 37^0C for 16-18 hours. The zone of inhibition was measured and interpreted as 2020 CLSI guidelines. For cefoxitin disc, zone diameter ≤ 21 mm was reported as MRSA and ≥ 22 mm as MSSA. (15) The antibiotic susceptibility data is analyzed in WHONET software (year 2020 version). As this laboratory used manual method of antimicrobial testing, vancomycin (minimum inhibitory concentration) was not reported for the year mentioned. Hence, regional data was used for vancomycin. The recommended anti-MRSA therapy is reviewed with the local antibiogram profile for anti MRSA agents. The same local data is incorporated in a clinical syndromic flow chart. Anti-MRSA agents are represented with color code in the syndromic antibiogram, as seen in Figure 1; blue color for agents with > 80% susceptibility (may be used empirically), red for agents with < 80% (not to be used empirically) and green for newer agents

recommended by international guidelines but not having local data. For annual updated guidelines and dosage or duration of treatment, readers are advised to refer to the local and or regional guidelines.

Statistical analysis – Not applicable

III. Results

Out of 160 isolates, 59, 90 and 11 isolates were from OPD, wards and ICU respectively. The overall prevalence of methicillin resistance during the study period was 36.25 per cent. Isolation rates for MRSA from outpatients and ward inpatients were 29 and 39 respectively. The data for ICU was not adequate to comment the MRSA rate. S. aureus isolates were from patients with skin and soft tissue infections, UTI, and lower respiratory infections in that order in both OPD and inpatients. There were no MRSA isolates from blood cultures. Susceptibility of 80 percent or more was considered for recommending empirical therapy for a given antimicrobial. Doxycycline showed more than 80% susceptibility compared to other antimicrobials among MRSA isolates. None were resistant to Teicoplanin and Linezolid. Cotrimoxazole, Erythromycin, Clindamycin and susceptibility was lower than 80 percent in both MSSA and MRSA. Nitrofurantoin susceptibility rates were more than 90% among both MRSA and MSSA isolates.

Table 1: Split antibiogram for MRSA and MSSA

Antimicrobials other than beta lactams	Methicillin Resistant *Staphylococcus aureus* – all specimen	Methicillin Sensitive *Staphylococcus aureus*– all specimen
	MRSA n= 58	**MSSA n=102**
1. GENTAMICIN	Less than 80%	**More than 90%**
2. COTRIMOXAZOLE	Less than 80%	**More than 80%**
3. ERYTHROMYCIN	Less than 80%	Less than 80%
4. CLINDAMYCIN	Less than 80%	**More than 80%**
5. DOXYCYCLINE	**More than 90%**	**More than 90%**
6. LINEZOLID	**More than 90%**	**More than 90%**
7. TEICOPLANIN	**More than 90%**	**More than 90%**

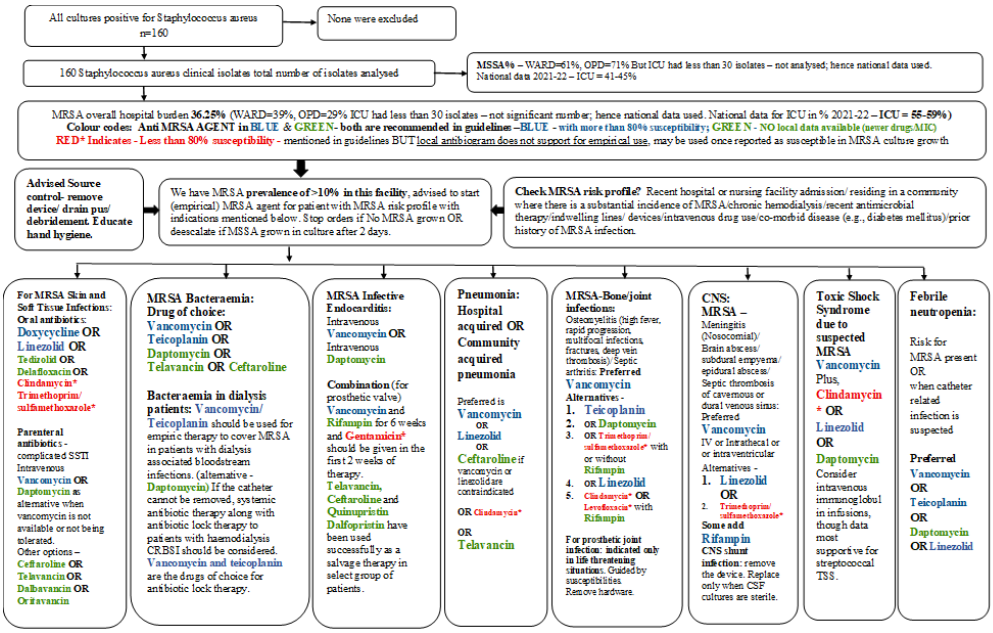

Figure 1*. Empirical treatment options for suspected MRSA infections with MRSA risk. (3,11–14) Uncomplicated cystitis or pyelonephritis due to MRSA is uncommon, and currently, there are insufficient data to recommend use of an MRSA-active agent for empirical therapy of uncomplicated UTI (10) However, in this facility Nitrofurantoin susceptibility rates were more than 90% among both MRSA and MSSA isolates. Data on antitoxic antimicrobials namely Clindamycin/Linezolid and polyclonal IVIG administration in management of Staphylococcal Toxic shock syndrome is from studies with a low level of evidence. (16)*

IV. Discussion

The study showed a MRSA rate of 36.25 percentage. This is in the same range as the national data. The overall MRSA rates (national data) have increased each year from 2017 to 2023 (32.9% to 43.7%). (8) The following anti – MRSA agents should be avoided in empirical treatment of MRSA in this facility for any

indication, they are Erythromycin, Azithromycin, Clindamycin, Gentamicin and Trimethoprim/ sulfamethoxazole. Among these, Erythromycin, Azithromycin are not recommended even in suspected MSSA infection. These agents have less than 80% susceptibility among both MSSA and MRSA isolates in this facility.

Skin and Soft Tissue Infections (SSTI): (7,17,18)

- This syndromic group has the clinical presentations highly variable in severity. Surgical drainage is the best treatment for any collection of pus. For cutaneous abscess, I&D likely to be sufficient. Incision and drainage are recommended over the use of antibiotics in simple cutaneous abscess or furuncle.
- Empiric MRSA cover should be used in all critically ill SSTI patients. For hospitalized patients with complicated SSTI (cSSTI; defined as patients with deeper soft-tissue infections, surgical/ traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns), in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for MRSA should be considered pending culture data. Vancomycin or teicoplanin should be the drugs of choice for empiric therapy for MRSA in complicated SSTI. Daptomycin/ceftaroline are other options for empiric therapy.
- Empiric MRSA cover should be also be considered in recurrent noncritical SSTI patients if they do not respond to previous therapy after sending appropriate cultures.
- Clinical and epidemiologic factors alone do not adequately predict the likelihood of MRSA infection. Definitive therapy depends on the susceptibility of the isolate and can include other drugs including clindamycin, cotrimoxazole, erythromycin or gentamicin. Note that these antimicrobials are having less than 80% susceptibility in this facility. Doxycycline is FDA-approved for the treatment of SSTI due to S. aureus, although not specifically for those caused by MRSA.
- The optimum duration of treatment for uncomplicated SSTIs should be one week. The optimum duration of treatment for complicated SSTIs should be 2–3 weeks.
- The use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTI is not recommended.
- Pediatric considerations: For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. Tetracyclines should not be used in children, 8 years of age. In hospitalized children with complicated SSTI, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with Linezolid may be initiated. Clindamycin may be used once culture test confirms susceptible isolate.

Bacteremia: (7,17,18)

- Vancomycin, is the drug of choice in all bacteremia's whether with or without complications. A vancomycin loading dose should be given to critically sick patients whenever there is MRSA risk.
- Intravascular devices should be removed whenever possible and blood cultures should be repeated every 48–72 h till negative. Infective endocarditis (IE) complicates 10–30% of all cases of Staphylococcus bacteremia. All bacteremia's in patients who have prolonged pyrexia, persistent positive blood cultures, history of valve disease, injection drug use, absence for any other focus for S. aureus bacteremia, prosthetic heart valves, cardiac pacemaker, those with abnormal results of transthoracic ECHO and those with clinical features of IE are to be evaluated for infective endocarditis using transesophageal echocardiography. If none of these complications are presented, and transesophageal echocardiography is still recommended after 5-7 days after initial detection of MRSA bacteremia.
- The entire duration of therapy should be by the intravenous route only. Follow-up cultures should be repeated to document clearance of the infection from the bloodstream. Persistent, positive cultures after 48 hours of treatment should prompt further evaluation related to drug susceptibility and source control.
- Vancomycin alternatives: The other alternatives need to be decided case by case basis and to be guided by susceptibilities once available. Daptomycin, Telavancin may be the alternative anti MRSA antibiotics for uncomplicated bacteremia. Teicoplanin may be considered over vancomycin in certain situations (e.g. vancomycin levels monitoring facility is not available/nephrotoxicity potential) based on the physician's discretion/experience.
- Infectious disease consultation has resulted in a better outcome in Staphylococcus bacteremia.
- **Bacteremia in dialysis patients:** About 30–50% of hemodialysis patients have a nasal carriage of MRSA. Vancomycin/teicoplanin should be used for empiric therapy to cover MRSA in patients with dialysis associated bloodstream infections. (alternative – Daptomycin) If the catheter cannot be removed, systemic antibiotic therapy along with antibiotic lock therapy to patients with haemodialysis CRBSI should be considered. Vancomycin and teicoplanin are the drugs of choice for antibiotic lock therapy
- **Endocarditis:** Drug of choice is Intravenous vancomycin. For patients who cannot tolerate vancomycin, intravenous daptomycin should be used. Recommended duration of treatment for native valve endocarditis is six weeks. Prosthetic valve endocarditis secondary to MRSA should be treated with intravenous Vancomycin

and Rifampin for 6 weeks and gentamicin should be given in the first 2 weeks of therapy. Clindamycin or Linezolid should not be used to treat endocarditis because of their poor outcome compared to cell wall active agents such as Vancomycin and Daptomycin.

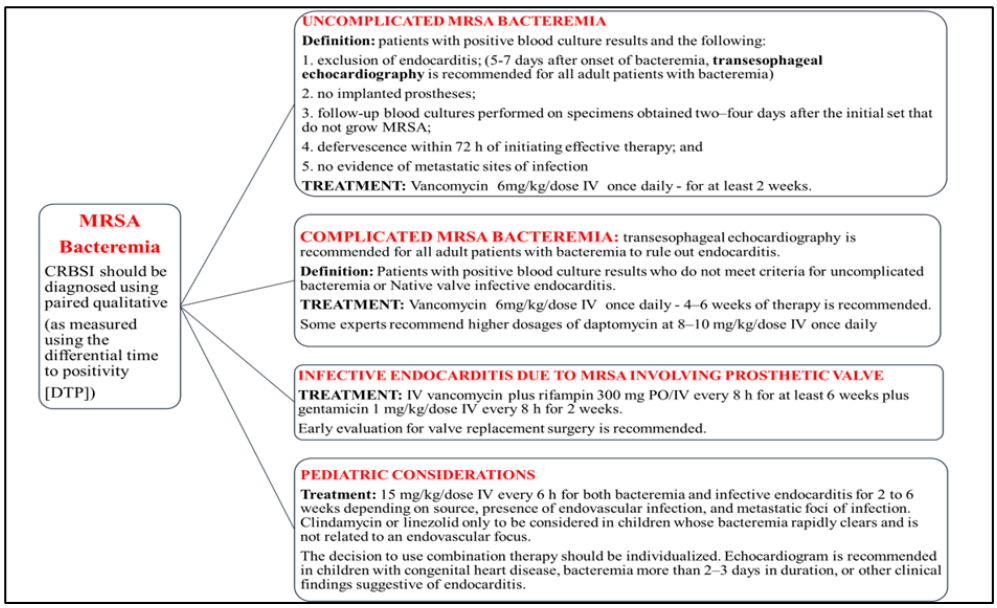

Figure 2. *Guidelines for MRSA bacteremia. All antimicrobials may be initiated empirically except for Clindamycin, which has less than 80% susceptibility in this facility. However, clindamycin may be considered if confirmed for MRSA growth and susceptibiity.*

Pneumonia: (7,17,18)

- Daptomycin cannot be used for pulmonary infections because it is inactivated by surfactant.
- Consider MRSA pneumonia in any patient with severe CAP (e.g., ICU admission, necrotizing/cavitary disease, empyema) pending sputum or blood culture results. For treatment, use susceptibilities to help guide final choice. Linezolid may have better PK/PD data in lungs compared to vancomycin; the study shows better initial clinical success than vancomycin, but similar 60d mortality.
- Drain or proceed with thoracic surgical consultation for empyema.
- Duration of therapy: 7-21d course, depending on severity; many cases of ventilator-associated pneumonia can be treated for 8d; necrotizing pneumonia usually requires longer courses ≥ 14d; bacteremic pneumonia, at least 14d.

MRSA-Bone/joint infections: (7,17,18)

- For, osteomyelitis (with high fever, rapid progression, multifocal infections, fractures, deep vein thrombosis) or Septic arthritis preferred anti-MRSA agent is intravenous vancomycin.
- There are other alternatives, such as Teicoplanin, Daptomycin and Linezolid as mentioned in the figure.
- Trimethoprim/ sulfamethoxazole or Clindamycin or Levofloxacin with or without Rifampicin may be used only after susceptible MRSA isolate is confirmed.
- For prosthetic joint infection empirical anti-MRSA is indicated only in life threatening situations, therapy should be guided by susceptibility. Advanced molecular diagnostics namely PCR and sequencing have been used successfully to diagnose as culture yield in these cases is low. The removal of implant strongly recommended by all guidelines.

Central Nervous System infective syndromes: (17)

- Anti-MRSA therapy is indicated in meningitis (Nosocomial), Brain abscess, subdural empyema, epidural abscess, septic thrombosis of cavernous or dural venous sinus. Preferred agent is Vancomycin either IV, Intrathecal or intraventricular.
- The alternatives being Linezolid OR Trimethoprim/ sulfamethoxazole (if culture confirms Trimethoprim/ sulfamethoxazole susceptible isolate). Some add Rifampin CNS shunt infection: remove the device. Replace only when CSF cultures are sterile.

Toxic Shock Syndrome due to suspected MRSA: (17)
- Drug of choice is intravenous Vancomycin with Clindamycin (if culture reports susceptible isolate).
- There are alternatives namely, Linezolid or Daptomycin.
- Consider intravenous immunoglobulin infusions, though data most supportive for streptococcal TSS.
- Data on antitoxic antimicrobials namely Clindamycin/Linezolid in management of Staphylococcal Toxic shock syndrome has been from limited studies with a low level of evidence.

Febrile neutropenia: (7)
- Considered only in institutions where MRSA is common or when catheter related infection is suspected.
- Preferred is Vancomycin OR Teicoplanin. Alternatives being, Daptomycin OR Linezolid.

Antibiotic lock therapy: (7)
- Antibiotic lock therapy should only be considered adjunct to systemic antibiotics when catheter salvage is being attempted in the setting of an active BSI, as opposed to routine prophylaxis.
- The stability/compatibility of the anticoagulant with the antibiotic should be considered. For example, EDTA or N-acetyl cysteine may be used to disturb the bacterial biofilm.
- Vancomycin and teicoplanin are the drugs of choice for antibiotic lock therapy.

Limitations of the study
1. The newer anti-MRSA agents; namely Ceftaroline, Telavancin, Dalbavancin and Oritavancin are not currently tested in this laboratory.
2. Lack of automation in antimicrobial susceptibility testing. Some anti-MRSA agents, namely Vancomycin, Daptomycin do not have disk diffusion clinical breakpoints. For this study duration, manual disk diffusion susceptibility testing.

V. Conclusion

The right empirical antimicrobial treatment always initiated along with good source control measures for managing both MRSA or MSSA infections. Appropriate clinical samples must to be sent for culture before the empirical treatment. Cost effective anti-MRSA alternatives should be explored. In this regard, the local antibiogram for MRSA isolates presented as syndromic flowchart can be useful tool. The local susceptibility data for the newer anti-MRSA agents with minimum inhibitory concentrations could enhance options for serious MRSA infections. In this regard, laboratory strengthening with automation and adequate skilled manpower can address the gaps in data. On the other hand, rigorous infection control practices and antimicrobial stewardship activities could reduce the MRSA prevalence. The treating doctor must justify empirical anti-MRSA treatment for definite indications. The microbiologist must timely update prevalent local bugs and their antibiogram preferably with clear clinical indications to reduce inappropriate antimicrobial use.

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