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MRSA: THE EVOLVING PATHOGEN, RECENT TRENDS IN DIAGNOSIS AND TREATMENT.

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ABSTRACT

MRSA is often used to describe multi-drug resistant *Staphylococcus aureus*. Resistance is mediated by a gene (*mecA*) that encodes the production of an altered penicillin-binding protein (PBP2a), which does not allow for the binding of ß-lactams to the bacterial cell wall, because ß-lactams exert antibacterial activity by binding and inhibiting enzymes necessary for bacterial cell wall synthesis, so these antimicrobials are not effective against MRSA. While infection control initiatives have stemmed the rising prevalence, MRSA remains a significant pathogen with its classified strains such as MRSA (CA-MRSA & HA-MRSA), VRSA (VISA-Intermediate & VRSA), MSSA, EMRSA (In Epidemiological settings), LA-MRSA (Live Stock).

ORIGINAL RESEARCH ARTICLE

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram-positive bacterium that is resistant to methicillin (a member of the penicillin family) and many other ß-lactam antimicrobials such as penicillin and cephalosporins. The description "methicillin-resistant" was first used in 1961, based on the discovery of a human *Staphylococcus aureus* infection in the United Kingdom that was resistant to methicillin.[1] Since that time, MRSA has emerged as a significant problem worldwide, and the term has evolved to include resistance to additional ß-lactam antimicrobials. The mechanism leading to methicillin resistance (MRSA) was finally identified in 1981.[2] Currently, the term MRSA is often used to describe multi-drug resistant *Staphylococcus aureus*. Resistance is mediated by a gene (*mecA*) that encodes the production of an altered penicillin-binding protein (PBP2a), which does not allow for the binding of ß-lactams to the bacterial cell wall, because ß-lactams exert antibacterial activity by binding and inhibiting enzymes necessary for bacterial cell wall synthesis, so these antimicrobials are not effective against MRSA.[3,4,5]. While infection control initiatives have stemmed the rising prevalence, MRSA remains a significant pathogen with its classified strains such as MRSA (CA-MRSA & HA-MRSA), VRSA (VISA-Intermediate & VRSA), MSSA, EMRSA-15, 16, 17 (In Epidemiological settings), LA-MRSA (Live Stock).[6]

2. Transmission

The horizontal transmission of methicillin resistance to Staphylococcus aureus (MRSA) in hospital and community settings and growing prevalence of these strains, presents a significant clinical challenge to the management of serious infections worldwide.[7] Community-associated MRSA strains occur in people who have not

been hospitalized or recently had invasive procedures. They first appeared in high risk populations (e.g., Patients in hospital for a long period of time, on kidney dialysis (haemodialysis), receiving cancer treatment or specific medications that affect immune function, Intravenous drug users, Individuals who have had surgery within a year of being back in hospital.).[8]

MRSA infections in humans are highly variable. MRSA may progress substantially within 24–48 hours of initial topical symptoms. After 72 hours, MRSA can take hold in human tissues and eventually become resistant to treatment. [9, 10]

Transmission also occurs through clothing such as 100% cotton, cotton terry (towels and wash cloths), polyester (privacy drapes and curtains), polypropylene plastic (splash aprons) and 40% polyester blend (scrub suits and lab coats).[11]

The 5 Cs can be used to remember what factors make it easier for MRSA to be transmitted Crowding, Contact (skin-to-skin)**,** Compromised skin (open wounds), Contaminated (items and surfaces) and lack of Cleanliness. [12]

3. Role in Disease

Community Acquired MRSA has emerged as significant pathogen, especially in children, prisoners, Intravenous Drug Users (although rates also increased in adults with no clear risk factors). Rarely, serious disease with or without necrotizing fasciitis may occur. CA-MRSA is also a cause of necrotizing pneumonia. Diagnosis is to be considered in a case of severe pneumonia with evidence of cavitation/necrosis, particularly after influenza like illness.

Staphylococcal toxic shock syndrome, caused by TSST-1 or other enterotoxin producing strains present with a constellation of fever, low BP, red rash and multi-organ failure. Risks include tampon use, nasal packing, surgical wounds. diarrhoea, ingestion of preformed Staphylococcal enterotoxin causes acute, self-limited gastroenteritis with an Incubation period of 2-6 hours.[13]

In the Bloodstream, the primary risk is presence of intravascular catheter, which should be removed immediately. Infection may occur without apparent focus or entry site; if without focus, we should evaluate for endocarditis (TTE/TEE), mycotic aneurysms or vertebral infection (discitis, osteomyelitis, epidural abscess). Skin/soft tissues infections include folliculitis, cellulitis, furuncle, carbuncle, abscess, impetigo (may occur in combination with *Streptococcus pyogenes*), Breast mastitis, Abscesses of spleen, kidney, epidural space; visceral or deep abscesses occur almost always due to hematogenous seeding from bacteremia. [14, 15] Endocarditis may occur in 6-25% of *S. aureus* bacteremia; Afflicts both native and prosthetic valves. [16, 17]

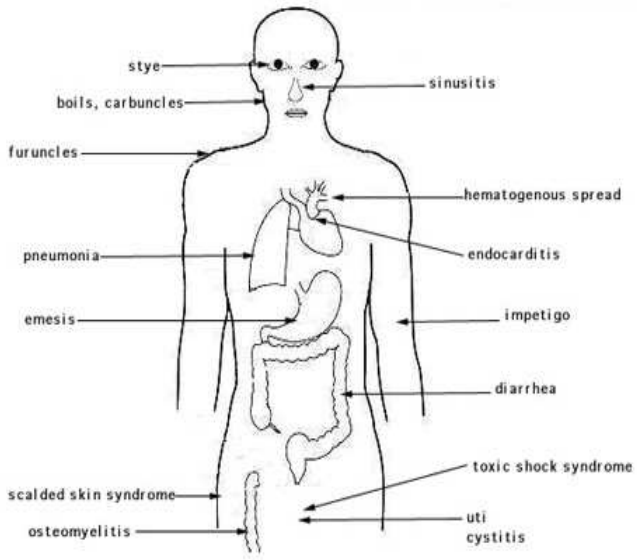
Bone pathologies include osteomyelitis (*S. aureus* leading cause, most common is vertebral osteomyelitis secondary to bacteremia/discitis), Prosthetic devices e.g., pacemaker leads and pocket, prosthetic joints.

MRSA strains are also responsible for Nosocomial pneumonia[18] , Septic pulmonary emboli which is associated with right-sided Endocarditis. [19], Mucosal surfaces related to release of TSST1 and subsequent toxic shock syndrome and Toxin associated gastroenteritis

CNS manifestations may be postoperative meningitis, meningitis associated with bacteremia/endocarditis. [20]

Common Clinical symptoms:

1. Acute bacterial skin and skin structure infections
   - A. Folliculitis
   - B. Furuncle (boil)
   - C. Carbuncle
   - D. Styes
   - E. Abscess
   - F. Impetigo
   - G. Paronychia
   - H. Wound infections
   - I. Cellulitis
2. Osteomyelitis
3. Endocarditis
4. Infections in Pacemaker Pockets/ Implants
5. Acute Food Poisoning due to toxins



Parts of the body and illnesses caused by a MRSA infection. MRSA has the ability of infecting multiple parts of the body, thus producing a variety of illnesses (Image from Todar, 2008).

4. Diagnosis

Depending upon the type and site of infection present, an appropriate specimen is obtained accordingly for definitive identification, either by using biochemical or enzyme-based tests. A Gram stain is first performed to guide the way, which should show typical gram-positive bacteria, cocci, in clusters. Second, the isolate is cultured on mannitol salt agar, which is a selective medium with 7–9% NaCl that allows *S. aureus to* grow, producing yellow-colored colonies as a result of mannitol fermentation and subsequent drop in the medium's pH. Furthermore, for differentiation on the species level Catalase (positive for all *Staphylococcus species), Coagulase (fibrin clot formation, positive for S. aureus), DNAse*(zone of clearance on DNase agar), Lipase (a yellow color and rancid odour smell) & Phosphatase (a pink color) tests are all done. For staphylococcal food poisoning, phage typing can be performed to determine whether the staphylococci recovered from the food were the source of infection. [21]

Rapid diagnosis and typing: Recent genetic advances have enabled reliable and rapid techniques for the identification and characterization of clinical isolates of *S.aureus* in real time. These tools support infection control strategies to limit bacterial spread and ensure the appropriate use of antibiotics. Quantitative PCR is increasingly being used to identify outbreaks of infection. [22 23] To observe the evolvement of *S. aureus and its ability to adapt to each modified* antibiotic, two basic methods known a "band-based" or "sequence-based" methods are employed. [24] With the reference of these methods other methods such as Multi-locus sequence typing (MLST), Pulsed-field gel electrophoresis (PFGE), Bacteriophage typing, spa locus typing & SCCmec typing are often conducted more than others. With these methods, it can be determined where the strains of MRSA originated and also where they are currently. [25]

5. Drugs: Principal Characteristics of Current US Food and Drug Administration–Approved Anti-infective Agents for Methicillin-Resistant Staphylococcus aureus. [26]

Agent	Bacterial Effect and Mechanism of Action	Route of Administration and Dosing Recommendations	Dosage Adjustment for Renal and Hepatic Impairment	Adverse Events	Advantages	Disadvantages
Vancomycin	"Slow" Bactericidal activity (concentration independent); cell wall inhibition	IV: 500 mg q6h or 1000 mg q12h; high-dose therapy (15 to 20 mg/kg total body weight q8 to 12 h) currently recommended when MIC values are 1 µg/mL	Renal: Dosing adjustments are necessary; dosing nomograms and monitoring trough serum vancomycin concentration recommended Hepatic: no adjustment needed	Nephrotoxicity; red man syndrome	Inexpensive; >50 y of clinical experience	VISA, hVISA, VRSA; increasing MIC values associated with poor outcomes; nephrotoxicity with higher doses
Linezolid	Bacteriostatic; Protein synthesis inhibition (23S RNA at 50S ribosomal subunit)	IV or PO: 600 mg q12h	Renal: None Hepatic: No specific recommendations	Thrombocytopenia and anemia (duration dependent); peripheral and optic neuropathy; lactic acidosis; serotonin syndrome	100% bioavailable oral formulation; good drug penetration into lung; active against VRE	Bacteriostatic; serious adverse events with longterm use (>14 d); increasing linezolid-resistant S. aureus; high drug cost
Daptomycin	Bactericidal (concentration dependent); membrane depolarization (Ca++ dependent)	IV: cSSSI: 4 mg/kg (total body weight) q24h; S. aureus bacteremia: 6 mg/kg (total body weight) q24h; some experts recommend higher doses (8 to 10 mg/ kg) for bacteremia/ infective endocarditis indications	Renal: For CrCl <30 mL/min, q48h Hepatic: No specific recommendations	CPK elevation; myopathy; peripheral neuropathy; case reports of rhabdomyolysis and eosinophilic pneumonia	Rapidly bactericidal; effective for MRSA bloodstream infections and right-side endocarditis; active against VRE; extensive published literature on treatment experiences for a wide range of MRSA infections	Inactivated by pulmonary surfactant and should not be used to treat pneumonia; increasing MIC values correlated to vancomycin increasing MIC values; suboptimal clinical outcomes in patients with reduced renal function; high drug cost

Tigecycline	Bacteriostatic; Protein synthesis inhibition (at 30S ribosomal subunit)	IV: loading dose of 100 mg followed by 50 mg q12h	Renal: None Hepatic: Child-Pugh class C, 100 mg single dose, maintenance 25 mg q12h	GI side effects (nausea and vomiting are common)	Active against VRE	Bacteriostatic; low serum and ELF drug concentrations; not approved for HAP/VAP; high rates of GI adverse events; higher risk of mortality than comparator agents; high drug cost
Telavancin	Bactericidal (concentration dependent); cell wall inhibition and membrane depolarization	IV: 10 mg/kg (total body weight) q24h	Renal: CrCl 30 to 50 mL/min, 7.5 mg/kg q12h; CrCl 10 to <30, 10 mg/kg q48h; CrCl <10, limited data Hepatic: No specific recommendations	GI side effects (including dysgeusia); mild QT prolongation; nephrotoxicity	Rapidly bactericidal against MRSA, VISA, and VRSA; active against MRSA strains resistant to vancomycin, linezolid, and daptomycin	Nephrotoxicity; lower clinical outcomes in patients with reduced renal function; REMS and avoid use during pregnancy; coagulation test interference; manufacturing issues limit its current availability
Ceftaroline	Bactericidal (time dependent); cell wall inhibition	IV: 600 mg q12h	Renal: CrCl 31 to 50 mL/min, 400 mg q12h; CrCl 15 to 30, 300 mg q12h; CrCl <15, 200 mg q12h Hepatic: No specific recommendations	Well tolerated (<5% incidence of diarrhea, nausea, rash)	Bactericidal; well tolerated; moderately expensive	Limited reports on treatment of MRSA infections other than ABSSSIs

a) Vancomycin, remains an acceptable treatment option for the management of MRSA and has remained the main stay of treatment ever since 1958. No drug to date has shown superiority to vancomycin in the treatment of MRSA infections with the possible exception of Linezolid in hospital-acquired pneumonia (HAP). Vancomycin AUC/MIC of 400 has been recommended in consensus guidelines to predict successful therapy, continuous infusion have been associated with lower rates of nephrotoxicity. [27]

b) Teicoplanin is a glycopeptide with a similar mode of action as vancomycin. Recent data and a meta-analysis both conclude that teicoplanin (at higher and appropriate dosing) is not inferior to vancomycin and may be associated with a lower rate of adverse events.

c) Lipoglycopeptides Oritavancin, telavancin, and dalbavancin are semi-synthetic lipopolypeptide analogues of vancomycin with activity against MRSA. In common with vancomycin, they each contain a heptapeptide core that enables inhibition of cell wall synthesis.

d) Anti-MRSA Cephalosporin's Discovery of two cephalosporins (β-lactams) >Ceftaroline >ceftobiprole with in-vitro activity against MRSA due to their affinity for the penicillin-binding protein PBP2a, offer great promise in the treatment of MRSA.

e) Daptomycin belongs to a new cyclic lipopeptide class of antibiotics and was first licensed for human use in 2003. It has a unique mechanism of action, with calcium-dependent binding to the cytoplasmic membrane resulting in rapid membrane depolarization and efflux of potassium. This results in the arrest of DNA, RNA, and protein synthesis and leads to rapid cell death. Importantly, daptomycin is inactivated by pulmonary surfactant and cannot be used in the treatment of pneumonia.[28]

f) Linezolid is an oxazolidinone class antibiotic that inhibits bacterial protein synthesis by preventing the formation of the 70S initiation complex with activity against MRSA. Unlike, vancomycin, linezolid achieves high levels in the epithelial lining fluid of the lungs, making it a promising candidate for treatment of patients with HAP, including MRSA.

g) Tedizolid (previously known as torezolid during early studies) It is a new oxazolidinone that has been specifically engineered to improve bioavailability and efficacy but reduce toxicity compared with linezolid. It is dosed once daily and its potency is 4 to 16 times greater than linezolid.

h) Quinupristin/Dalfopristin (QD) is a combination of two semi-synthetic streptogramin antibiotics (derived from pristinamycin) in a ratio of 30:70. QD binds to the 50S bacterial ribosome in two sequential steps, and thus inhibits bacterial protein synthesis. Each drug alone is bacteriostatic against susceptible gram-positive organisms including MRSA, but the combination is synergistic and bactericidal.

i) Tigecycline is a parenteral glycylcycline antibiotic, derived from minocycline. It has in vitro activity against many gram-positive bacteria, including MRSA. The main treatment-limiting adverse effect of tigecycline is nausea and vomiting, which occurs in 30 to 40% of treated patients.

Several investigational agents with activity against drug-resistant gram-positive pathogens are being developed primarily for treatment of MRSA infections, including tedizolid, dalbavancin, and oritavancin.[29]

6. Prevention

Screening programs

Patient screening upon hospital admission, with nasal cultures, prevents the cohabitation of MRSA carriers with non-carriers, and exposure to infected surfaces.

Alcohol has been proven to be an effective surface sanitizer against MRSA. Quaternary ammonium can be used in conjunction with alcohol to extend the longevity of the sanitizing action. Non-flammable alcohol vapour in carbon dioxide systems do not corrode metals or plastics used in medical environments.

- **Hand washing**, alcohol-based and chlorhexidine basedrubs remain somewhat effective.
- **Prevention for health care workers**, wearing gloves when examining or treating body areas with a suspected cutaneous lesion; and proper hand washing following examination or treatment is required, including proper hand hygiene; gloving; wearing eye, mouth, and nose protection; gowning; cleaning equipment with disinfectant; and the appropriate cleaning of laundry.
- The CDC recommends that surfaces and floors be cleaned with disinfectants approved by the Environmental Protection

Agency using List-H on the Environmental Protection Agency's list.

7. The burden of disease

S. aureus infections have been associated with significant morbidity and mortality, since it was first being identified In the pre-antibiotic era, bloodstream infections due to S. aureus yielded more than 80% mortality. Although the prognosis has since improved, the impact of the disease remains dramatically high.

Contemporary studies have shown that overall in-hospital mortality rates for patients with bloodstream infections due to MRSA are in the range of 30% but can be as high as 65% in some centers. This mortality number is higher than the rates of death produced by human immunodeficiency virus, viral hepatitis, tuberculosis, and influenza combined.

Indian scenario: The Prevalence of MRSA varies between regions and between hospitals in the same region as seen in a study from Delhi where the MRSA prevalence in nosocomial SSTI varied from 7.5 to 41.3 per cent between three tertiary care teaching hospitals. [30]

Recommendations for the Treatment of Methicillin-Resistant Staphylococcus aureus (MRSA)

Manifestation	Treatment	Adult dose
Skin and soft-tissue infection (SSTI)		
Abscess, furuncles, Carbuncles	Incision and drainage	
Purulent cellulitis (defined as cellulitis associated with purulent drainage or exudate in the absence of a drainable abscess)	Clindamycin	300–450 mg PO TID
	TMP-SMX	1–2 DS tab PO BID
	Doxycycline	100 mg PO BID
	Minocycline	200 mg 3 1, then 100 mg PO BID
	Linezolid	600 mg PO BID
Nonpurulent cellulitis (defined as cellulitis with no purulent drainage or exudate and no associated abscess)	b-lactam (eg, cephalexin and dicloxacillin)	500 mg PO QID
	Clindamycin	300–450 mg PO TID
	b-lactam (eg, amoxicillin) and/or TMP-SMX or a tetracycline	Amoxicillin: 500 PO mg TID See above for TMP-SMX and tetracycline dosing
	Linezolid	600 mg PO BID
Complicated SSTI	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Linezolid	600 mg PO/IV BID
	Daptomycin	4 mg/kg/dose IV QD
	Telavancin	10 mg/kg/dose IV QD
	Clindamycin	600 mg PO/IV TID
Bacteremia and infective endocarditis		
Bacteremia	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Daptomycin	6 mg/kg/dose IV QD
Infective endocarditis, native valve	Vancomycin and Daptomycin	

Infective endocarditis, prosthetic valve	Vancomycin and gentamicin and Rifampin	15–20 mg/kg/dose IV every 8–12 h 1 mg/kg/dose IV every 8 h 300 mg PO/IV every 8 h
Persistent bacteremia		
	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Linezolid	600 mg PO/IV BID
	Clindamycin	600 mg PO/IV TID
Bone and joint infections		
Osteomyelitis	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Daptomycin	6 mg/kg/day IV QD
	Linezolid	600 mg PO/IV BID
	Clindamycin	600 mg PO/IV TID
	TMP-SMX and Rifampin	3.5–4.0 mg/kg/dose PO/IV every 8–12 h
Septic arthritis	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Daptomycin	6 mg/kg/day IV QD
	Linezolid	600 mg PO/IV BID
	Clindamycin	600 mg PO/IV TID
	TMP-SMX	3.5–4.0 mg/kg/dose PO/IV every 8–12 h
Prosthetic joint, spinal implant infections	Please see text	
Central nervous system infections		
Meningitis	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Linezolid	600 mg PO/IV BID
	TMP-SMX	5 mg/kg/dose PO/IV every 8-12 h
Brain abscess, subdural empyema, spinal epidural abscess	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Linezolid	600 mg PO/IV BID
	TMP-SMX	5 mg/kg/dose PO/IV every 8–12 h
Septic thrombosis of cavernous or dural venous sinus	Vancomycin	15–20 mg/kg/dose IV every 8–12 h
	Linezolid	600 mg PO/IV BID
	TMP-SMX	5 mg/kg/dose PO/IV every 8-12 h

8. Recent Trends

Vancomycin resistance has become evident in select clinical settings through rising MICs, growing awareness of hetero-resistance and emergence of intermediate-resistant and fully resistant strains. While resistance to linezolid and daptomycin remains low overall, point mutations leading to resistance have been described for linezolid, and horizontal transmission of cfr-mediated

resistance to linezolid has been reported in clinical isolates. These resistance trends highlight the ongoing need for new and more potent antimicrobial therapies.

9. Conclusion

For Determining the optimal methods of treating this evolving organism, it is required that both clinicians and researchers understand the organism better. Vancomycin remains a viable option, but despite this antibiotic being in clinical use for over 50 years, there still remains uncertainty about the best dosing strategy. Lipoglycopeptides as a class, all the agents show in vitro potency greater than Vancomycin. However, their long half life and complex pharmacokinetics may preclude these agents being used in critically ill patients. Anti-MRSA cephalosporins (Ceftobiprole and Ceftaroline) provide greater promise in the treatment of MRSA. Ceftabiprole is a viable option in the treatment of community acquired pneumonia(CAP) and HAP. Daptomycin is currently the only antibiotic to have shown non-inferiority to Vancomycin in the treatment of MRSA bacteremia. The drugs till date have shown superiority to Vancomycin in the treatment of MRSA with possible exception of Linezolid in HAP. There has been an increase in the number of agents available for treatment of MRSA; the exact role and choice of agents need to be defined.

Methicillin-resistant Staphylococcus aureus (MRSA) continues to be associated with significant morbidity and mortality. **Vancomycin was the "gold standard" of treatment** for serious MRSA infections; however, the emergence of less-susceptible strains, poor clinical outcomes, and increased nephrotoxicity with high-dose therapy **are challenging its current role** as first-line therapy.

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