Drug treatment of MRSA infections

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INTRODUCTION

MRSA (Methicillin Resistant Staphylococcus aureus) has been a pathogen linked to health care facilities and is a major cause of health care associated infections. More recently, CA-MRSA (Community acquired MRSA) strains have been found to cause infection in patients with no risk factors for HA-MRSA (Hospital associated MRSA). The Center for Disease Control and prevention (CDC) reports that about one percentage of the general public is infected with this superbug.

Although 50-60% of patients with MRSA are merely colonised, serious infections such as those involving the blood stream, respiratory tract and bone or joints do occur. As per the guidelines released by the Infectious diseases society of America (IDSA) for treatment of MRSA, it is the predominant cause of skin infections among patients presenting to the emergency room.

These infections are more difficult to treat than infections caused by methicillin susceptible isolates and MRSA spread easily among patients in hospitals. The toxicity of these pathogens and limited effectiveness of available treatment have led to high mortality rates and vast expenses caused by prolonged hospitalisation and usage of additional antibiotics.

Community acquired MRSA strains emerged in late 1990 to 2000, infecting healthy people who had not been in contact with health care facilities. CA-MRSA differs from HA-MRSA in its genetic make-up, increased pathogenicity and susceptibility to antibiotic treatment.

Community acquired MRSA is more easily treated and is more virulent than Hospital acquired MRSA. The genetic mechanism for the enhanced virulence in CA-MRSA remains an active area of research. Panton-Valentine leukocidin (PVL) genes are especially of interest because they are an unique feature of CA-MRSA.

The resistance of MRSA to beta-lactam antibiotics is due to the presence of the mecA gene sequence. The mecA gene produces trans peptidase PBP2a (penicillin-binding protein) that decreases the bacterial affinity of the beta-lactam antibiotics. The mecA gene is a subset of a larger SCCmec gene (Staphylococcal Cassette Chromosome mec gene), the genetic element that carries the mecA gene encoding methicillin resistance.

Several variations of the SCCmec gene have been sequenced. SCCmec gene types I, II and III are found in HA-MRSA, whereas CA-MRSA bacteria have the SCCmec type IV gene. This difference may explain the continued susceptibility of CA-MRSA compared with HA-MRSA to some oral antibiotics such as trimethoprim-sulfamethoxazole etc.

Drug treatment

Both CA-MRSA and HA-MRSA are resistant to traditional anti-staphylococcal beta-lactam antibiotics. CA-MRSA has a greater
spectrum of antimicrobial susceptibility, including Sulfa drugs (like Co-trimoxazole), Tetracyclines (like Doxycycline and Minocycline) and Clindamycin (for osteomyelitis), Vancomycin is the drug of choice for treating CA-MRSA, according to a Henry Ford Hospital Study. HA-MRSA is resistant even to these antibiotics and often is susceptible only to Vancomycin.

Newer drugs, such as Linezolid and Daptomycin, are effective against both CA-MRSA and HA-MRSA. Ceftaroline and Ceftobiprole, new fifth generation cephalosporins, are the first beta-lactam antibiotics approved in the US to treat MRSA infections (skin and soft tissue only).

Vancomycin and Teicoplanin: These are Glycopeptide antibiotics used to treat MRSA infections. Teicoplanin is a structural congener of Vancomycin that has a similar activity spectrum but a longer half-life. Because the oral absorption of Vancomycin and Teicoplanin are very low, these agents must be administered intravenously to control systemic infections.

Treatment of MRSA infection with Vancomycin can be complicated due to its ototoxicity and nephrotoxicity. Moreover, many clinicians believe that the efficacy of Vancomycin against MRSA is inferior to that of anti-staphylococcal beta-lactam antibiotics against methicillin-susceptible Staphylococcus aureus (MSSA).

Several newly discovered strains of MRSA show antibiotic resistance even to Vancomycin and Teicoplanin. These new evolutions of the MRSA bacterium have been dubbed Vancomycin intermediate-sensitive Staphylococcus aureus (VISA). Linezolid, Quinupristin/ Dalfopristin, Daptomycin, Ceftaroline and Tigecycline are used to treat more severe infections that do not respond to Glycopeptides such as Vancomycin. Current guidelines recommend Daptomycin for VISA bloodstream infections and endocarditis.

Linezolid: A synthetic antimicrobial agent of Oxazolidinone class and is effective against gram positive organisms. By binding to the 23S fraction of the 50S ribosomal subunit, it inhibits bacterial protein synthesis. Resistance is due to the modification of the ribosomal binding site and has been reported clinically among enterococci and MRSA strains. It has good oral bioavailability.

It is generally well tolerated with only minor side effects. Thrombocytopenia has been reported and is related to duration of therapy. So platelet should be monitored in patients with risk of bleeding. Linezolid is a weak monoamine oxidase inhibitor. Patient receiving concomitant therapy with an adrenergic or serotonergic agent may experience an enhancement of drug effects. It should be reserved as an agent of last resort for treatment of infections caused by multiple drug resistant strains. Indiscriminate use and overuse will hasten selection of resistant strains and the eventual loss of this valuable new agent.

Daptomycin: A cyclic lipopeptide antibiotic was recently revisited because of the growing difficulty in treating resistant gram positive organisms especially Vancomycin resistant gram positive strains. Daptomycin, by binding to the cytoplasmic membrane causes cell death. It has a concentration dependent bactericidal activity. Due to its unique mechanism of action it does not produce any cross resistance. There are no known...
resistance mechanisms also. It is poorly absorbed orally and should only be administered intravenously. Direct toxicity to muscle precludes IM injection. It needs only once daily dosing. Approximately, 80% of the administered dose is excreted unchanged in urine. Dose adjustment is required for creatinine clearance below 30 ml/mt. Skeletal muscle damage has occurred in animals. Elevation of creatine phosphokinase has been noted in humans. Caution should be taken during co administration with aminoglycosides and statins.

Quinupristin/Dalfopristin: These were described in the earlier issue of this journal. (Kerala Journal of Orthopaedics 2013;26(1):81-82)

Tigecycline: It is a Glycylcycline derivative of Tetracycline antibiotic, active against many drug resistant strains of both gram positive and gram negative bacteria. Its spectrum also includes anaerobes. Tigecycline circumvents the two major mechanisms of Tetracycline resistance, i.e., drug efflux and ribosomal protection. It is formulated for IV administration only. In addition to the Tetracycline class effect, chief adverse effect is nausea. Tigecycline can cause permanent tooth discoloration and should not be used in young children and pregnant women. It is FDA approved for treatment of skin

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Table 1. An overview of drugs used in MRSA infections
and skin structure infections and intra-abdominal infections.

Telavancin: This is a lipoglycopeptide antibacterial agent exhibits potent activity against MRSA isolates with reduced susceptibility to Vancomycin. The plasma half-life is 8 hrs, which supports once daily intravenous dosing.

Ceftaroline & Ceftobiprole: These new fifth generation Cephalosporins are the first beta lactam antibiotics to be effective against MRSA. Both have increased binding to Penicillin binding protein 2a, which mediates methicillin resistance in staphylococci, resulting in bactericidal activity against these strains.

Mupirocin: Perioperative prophylaxis with nasal Mupirocin can reduce the incidence of MRSA skin and soft tissue infections after orthopaedic surgery, probably by reducing nasal MRSA carriage in the endemic setting, without selecting for Mupirocin resistance.

**DISCUSSION**

There is an increase in the incidence of resistant bacterial strains causing osteomyelitis, arthroplasty infections and purulent arthritis in orthopaedics. Antibiotic treatment in Orthopaedics has a predominantly supportive status, surgical intervention is regarded as primary. Rational administration of antibiotics can markedly affect the subsequent course of the infectious process and also the prognosis of the disease.

Bone and joint infections caused primarily by gram positive pathogens such as aureus and to a lesser extent Enterococcus faecalis are difficult to treat successfully. Surgical intervention and prolonged courses of antibiotics are frequently required, and failure of first-line antibiotic therapy is common. The emergence of S. aureus strains with reduced susceptibility to Vancomycin, the long standing gold standard for bone and joint infections, has complicated the clinical scenario.

Few randomised trials comparing the efficacy of different antibiotics for bone and joint infections exist. Daptomycin, a novel intravenous lipopeptide antibiotic, has shown potent in-vitro activity against a broad spectrum of gram-positive bacteria, including many resistant pathogens commonly associated with bone and joint infections such as MRSA and Vancomycin resistant E. faecalis.

Early clinical investigation of Daptomycin in bone and joint infections unresponsive to antibiotics such as Vancomycin, has found a cure rate of approximately 80%, with a low incidence of adverse events and drug resistance. Thus Daptomycin is a promising option for patients with bone and joint infections such as MRSA osteomyelitis.

Costs of Linezolid therapy are higher than that of Vancomycin, but Linezolid brings into practice many advantages compensating this economical aspect. Availability of oral dosage forms with reliable bioavailability creates the possibility of ambulatory treatment and increases the patient compliance. This will shorten the hospital stay thus reducing final treatment costs.

**CONCLUSION**

Despite the emergence of resistant and multidrug-resistant S. aureus, we have certain effective drugs in clinical use for which little resistance has been observed: Vancomycin, Quinupristin, Dalfopristin, Linezolid, Tigecycline, Telavancin, Ceftaroline and Daptomycin. However, Vancomycin is less effective for infections with MRSA isolates that have a higher MIC within the susceptible range.

Linezolid is probably the drug of choice for the treatment of complicated MRSA skin and soft tissue infections (SSTIs). Daptomycin has shown to be non-inferior to either Vancomycin or ß-lactams in the treatment of staphylococcal SSTIs, bacteremia and right sided endocarditis. Tigecycline was also non-inferior to comparator drugs in the treatment of SSTIs, but there is controversy about whether it is less effective than other therapeutic options in the treatment of more serious infections. Telavancin has been shown to be non-inferior to Vancomycin in the treatment of SSTIs and pneumonia, but has greater nephrotoxicity.

Ceftaroline is a broad-spectrum cephalosporin with activity against MRSA. It is non-inferior to Vancomycin in the treatment of SSTIs. Clindamycin, Trimethoprim-Sulfamethoxazole, Doxycycline, Rifampicin and Minocycline are oral anti-staphylococcal agents that may have utility in the treatment of SSTIs and osteomyelitis, but the clinical data for their efficacy is limited.

There are also several drugs with broad-spectrum activity against gram-positive organisms that have reached the phase II and III stages of clinical testing. They will hopefully be approved for clinical use in the upcoming years. They are Oritavancin, Dalbavancin, Omadacycline, Tedizolid, Delafloxacin, and JNJ-Q2.

Thus, there are currently many effective drugs to treat resistant S. aureus infections and many promising agents in the pipeline. Nevertheless, S. aureus remains a formidable
adversary, and despite our deep bullpen of potential therapies, there are still frequent treatment failures and unfortunate clinical outcomes.

REFERENCES


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