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Research Article

Overview of Antibiotic Therapy to Methicillin Resistant *Staphylococcus Aureus* (MRSA)

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ABSTRACT

Multidrug resistant Staphylococci are considered to be a major issue in human health. The MRSA strains shows great resistance to most commonly used antibiotics such as Aminoglycosides, Microlides,Fluoroquinolones and Chloramphenicol etc. Strains of S.*aureus* when recognized as MRSA,it is placed under the category of MDR and are labeled as superbug in the health domain.The genomic island Staphylococcal cassette chromosome make (SCC mec) contains the antibiotic resistant gene mec A along with Cytolycin gene psm-mec. High usage of antibiotics in hospitals with selection pressure of the antibiotics has led to the development of multidrug resistance (MDR) in hospital acquired MRSA (HA-MRSA) strains.

Keywords: methicillin, *Staphylococcus aureus*

INTRODUCTION

MRSA (Methicillin Resistant *Staphylococcusaureus*) is a Gram positive bacterium that is usually developed through horizontal gene transfer and also through natural selection. MRSA is one of the most usual cause of nosocomial infections[1]. Methicillin resistance strain of bacterium S.*aureus* was discovered in 1961.

The most common cause of MRSA is due to nosocomial infections. There are two ways through which MRSA can be acquired i.e. either through Hospital Acquired or through Community Acquired. It has been observed that Community acquired MRSA are resistant to fewer antibiotics than MRSA hospital acquired[2]. MRSA shows resistance to most of the antibiotics especially to the Beta-Lactam antibiotics. MRSA is not only spread through surgical wounds but also through non-surgical wounds like Ulcers[3], burns and traumatic wounds.

The nostrils and mucous membranes of the upper respiratory tract are typical sites of colonization from which nosocomial spread mayoccur[4]. As MRSA is resistant to most of the antibiotics specially the Beta-lactam antibiotics, Vancomycin being a glycopeptide is used for the treatment of such infections. Many such drugs like Linezolid, Daptomycin, Telavancin and Ceftaroline have been approved to treat the infections caused due to drug resistant Gram positive pathogens to overcome the limitations of Vancomycin[1].

Pathogenesis of MRSA infection

S. *aureus* is considered to be one of the most important bacterial pathogen with its ability to cause skin and soft tissue infections (SSTIs), surgical site infections, pyogenic lesions including various organs, hospital outbreak and community acquired infections[5]. There are certain strains of S.aureusthat show resistance to Beta-Lactam antibiotics that are used in hospitals and are called as MRSA[6].

Being a part of normal microbiota, the S. *aureus* are usually present in the upper respiratory tract and on the skin as well as in the gut mucosa. The basic symptom of bacterial infections is pain which is due to its invasions. In case of MRSA, the pain caused is due to virulence dependent agr and the bacterial pore forming toxins (PFTs).

TRPV1, cation channel that mediates heat hyperalgesia acts as a major pain modality. The PFT consists of three classes namely, alpha-hamolysin (Hla); phenol-soluble modulins (PSMs); leucocidin (HlgAB). These are responsible to cause pain by inducing the neuronal stimulation. It has been hypothesized that neurons producing pores allows the entry of QX-314 which is a membrane impermeable sodium channel blocker into the noiceptors that are peripheral sensory neurons that mediate pain and express TRP (Transcient Receptor Potential) to alleviate the pain during infections more significantly than the most commonly used analgesic treatment. The S. *aureus* are also capable of directly activating the sensory neurons causing pain independent of immune system and it was found that N-formylated peptides and Hla-induced calcium influx sensory neurons in vitro. Wild type S. *aureus* cause more thermal and mechanical hyperalgesia than the *S. aureus*Hla mutants. According to a study that defined the role for the quorum sensing accessory gene regulator (agr) system and its control of PFTs it was found that PSMs and LeukocidinHlgAB could produce pain when infected into mice.

In order to study the spontaneous pain by MRSA (USA 300) was used to infect mice with different doses of it into the hind paw ($5x10^6$-$5x10^8$cfu). An USA 300 is a clone of virulent community acquired MRSA that can cause skin and soft tissue infections. The study reflected spontaneous filching of paw over 1 hour and this was considered to be

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a feature for the sharp, spontaneous pain that human feels during local bacterial infections. It is observed that the spontaneous pain peaked observed that the spontaneous pain peaked at 20-30 mins post infection and remain at lower level upto 60 mins post infection. The spontaneous pain repeals when *S. aureus* were killed at 100ºC for 15 mins prior infection showing dependency on the factors of live bacteria[7].

Two virulent strains of MRSA; USA 300 and USA 500 were also compared to study their ability to produce pain and it was concluded that both of the strains produce significant levels of spontaneous pain with similar magnitude. The bicomponent agr quorum sensing system is activated in the transition from late exponential phase to stationary phase of growth that can detect bacterial density via auto inducer peptide controlling the expression of the virulent factors of S. *aureus.* The study (Kimbria J. Blake et al; 2018) depicts that the spontaneous pain repeals in mice infected with USA 300 mutant for the agr locus than to WTUSA 300 that was due to factors controlled by agr. It has been summed up that all three classes of agr dependent PFTs (Hla, Leukocidin, PSMs) can cause neuronal activation and produce spontaneous pain when injected into mice but in case of live bacterial infections, only Hla is necessary for inducing the spontaneous pain. Thermal hyperalgesia in S. *aureus* mediated by TRPV1, absence of agr did not make any affect of mechanical or hyperalgesia during infection when compared to WT bacteria. TRPV1 is activated by noxious heat and acts as a crucial mediator of heat hyperalgesia in inflammatory pain. The mice were treated with high dose of TRPV1-expressing nerve fibres and neurons. Simultaneously the QX-314 were studied to silent the pain during live USA 300 infections. As QX-314 is a positively charged quarternary derivative of Lidocaine, a comparison was made between the two analgesics in their ability to treat S. *aureus* induced pain. Lidocaine and QX-314 was injected in USA300 infection to study the intensity of decreased spontaneous pain and observed that both could reduce the pain caused by S. *aureus*[7].

The next category of analysis was made on mechanical and thermal hyperalgesia where 2% of QX-314 could induce blockade of mechanical hypersensitivity for upto 7 hours post infection along with blockade of heat hyperalgesia (~3 hours) whereas Lidocaine has no effect on both mechanical and thermal hyperalgesia[7].

A wide range of antibiotics are used to treat MRSA[8] including Beta-Lactam (Cephalosporin), glycopeptides antibiotic (Vancomycin, Teicoplanin) Clindamycin, Trimethoprim-Sulfamethoxazote(TMX-SMX), Rifampin, Telavancin etc. as the motive of antibiotics is to destroy or prevent the growth by various mechanisms. The working of the intervention basically prevents the spread of MRSA infection or treat the existing condition. Different types of interventions were considered such as comparison between antibiotic treatments versus no antibiotic treatment with different dose etc and with these two types of outcomes measures were followed: Primary Outcomes- all cause mortality, serious events (ICH-GCP 1996) and quality of life. Secondary Outcomes- duration of stay in hospital, healthcare resources usage, eradication of MRSA at maximal follow-ups, time required to heal the wound[9].

*Characteristics of SCC*Mec *elements*

SCC*mec* is a mobile genetic element that carries *mecA* (methicillin-resistant gene) and other functional genes. The *mec* gene sequences have the ability to enter into the bacteria sequences at 3 different points of the genome of *S aureus*. Gene transfer through conjugation involving the transposon "Tn-1546" with mecA gene encode modified penicillin binding protein showing resistance to methicillin and also to other penicillin derivatives. The gene *mec* A encodes for the penicillin binding protein PBP2a that cannot be bound by Beta – Lactam antibiotics and thus prevents the disruption of call wall formation by such antibiotics. Therefore, the mec gene is located on the genetic element called "Staphylococcal cassette chromosome "(SCC-mec)

When the antibiotic binds to the protein which prevents peptidoglycan synthesis in the cell wall of bacteria, it confers resistance. There are some bacteria that can produce a "Modified penicillin binding protein" that ceases to bind to antibiotic that prevents targeted effects of the antibiotic. Hence, their resistance of *S. aureus* to Beta-Lactam antibiotics is due to the presence of gene mecA[10]

Efficacy of anti-MRSA antibiotics

Many anti MRSA antibiotics are being in use however Vancomycin or Daptomycin are the two antibiotics that are considered the most for the treatment of MRSA infection. Along with it, certain alternative agents are also used for the salvage therapy.

Vancomycin: It is considered to be the most commonly preferred for the treatment of MRSA infection. Certain monitoring of serum concentration is associated to achieve the pharmakinetics/pharmacodynamics target[1]. It is a glycopeptide with branched glycosylated tricyclic peptide. It functions by binding to the growing end of peptide chains and preventing their interaction with transpeptide enzyme. According to few reports, VRSA (Vancomycin resistant S. *aureus)* showed MIC>32 microgram/ml where four VRSA with VanA gene from USA between 2002-2006 were reported. In 2006 VanA negative VRSA was reported byTiwari *et al*; 2006[11]. The MIC of the Vancomycin intermediate S. *aureus* (VISA) is between 8-16 microgram/ml which was reported in the year 1997 in Japan[6].

Daptomycin:It is a lipopeptide class antibiotic which works on calcium dependent binding and disrupts the cell membrane of the bacteria. It is a very rapid bactericidal agent as it is being prescribed once daily dose[6]. Because it has got a lipophilic behavior, it enters into the alveolar surfactant and gets deposited in the alveoli thereby resulting in eosinophilic pneumonia and hence reduces its therapeutic use. Currently it is the only antibiotic that shows non-inferiority to Vancomycin for the treatment of MRSA[1].

Teicoplanin:It is glycopeptide and it is used usually used as a drug for the initial treatment of MRSA or for the patients that show some kind of intolerance towards Vancomycin[6]. It has got slow bactericidal activity, efficacy and a slow spectrum of activity. However, there is a low

risk of nephrotoxicity with Teicoplanin when compared with Vancomycin[1].

Resistance to newer antibiotics

The prodrug of Ceftaroline namely Ceftaroline fosamil is a new broad spectrum. Cephalosporin that has been recently approved in USA for treating the acute bacterial skin and skin structure infections (ABSSSIs) and also community acquired bacterial pneumonia (CAPB). The antibiotic Ceftaroline is known with its potent *in vitro* activity against Gram-positive organism like MRSA and *Streptococcuspneumonia* as well as Gram negative organisms.According to their study, observed that none of their isolates showed resistance to ceftaroline. Clark *et al;* 2011 reported that prolonged selection in the presence of ceftaroline showed no evidence of resistance with other class of antibiotics[12].

The resistance pattern of Vancomycin, Teicoplanin and Daptomycin was also studied and it was found that none of the isolates showed resistance to Vancomycin and Teicoplanin however two isolates showed resistance to Daptomycin. According to Biedenbach *et al;* 2007, 3.2% rate of tolerance towards Vancomycin and 31.6% rate of tolerance towards Teicoplanin.It has been reported that there is a reduced susceptibility to vancomycin when associated with reduced susceptibility to Daptomycin[13]. According to Maria *et al* 2009, Daptomycin were more potent in vitro than vancomycin and Teicoplanin against MRSA[14]. According to Krause *et al,*2008 Stelavancin is more active than Vancomycin and Teicoplanin against all organisms tested with equal or greater potency to Daptomycin and Linezolid against all strain types except the VanA-type Vancomycin Resistant Enterococci (VRE)[15].

The antibiotic Mupirocin derived from *Pseudomonas fluorescens* is a topical antibiotic widely used for the treatment of MRSA associated skin and soft tissue infections[10]

Alternative approach for anti MRSA treatment (Bioactive compounds and phytoconstituents)

Among the 120 families & 130000 species of plants in India, there are many of them which are used in the treatment of various kinds of diseases. According to a recent research, the in vitro antimicrobial activity against MRSA has been found in Acorus *calamus*, Lawsonia *inermis*, Hemidesmus *indicus*, Holarrhea *antidyssentrica*, Punica *granatum*, etc.*A. calamus* commonly known as sweet flag that grows in the hills of the North Eastern region of India.It has been researched that the rhizome has got effects on the nervous system and are being used as antihypertensive, anti-anxiety, anticonvulsant and also for chronic diarrhea etc., along with certain bactericidal activity from its rhizome and leaf extracts. Triphala, a polyherbal Ayurvedic medicine in an anticancer, antimicrobial, antioxidant used in the treatment of mal-absorption, hyperglycemia and many other health diseases. Based on certain evidences & animal model, each part of Triphala has the property of Anti MRSA[6].

There are also few phyto-constituents that have the anti MRSA activity. Certain parts of a variety of plants are used to obtain their extract into a solvent form and these extracts undergo phytochemical analysis to report the presence of certain medicinal compounds along with anti MRSA activity. Beta-asarone from Acorus *calamus* rhizome, Mansonone from Ulmus *davidiana* is few important ones[6].

CONCLUSION

The optimal salvage regimen for persistent MRSA bacteria is uncertain and thus the treatment of MRSA bacteremia requires prompt source control and initiation of active antimicrobial therapy. The need for antibiotics that are more efficacious than Vancomycin has never been greater, however, several agents have become available for treating MRSA. There are also certain plants that are being traditionally used as medicines are the source of bioactive phytoconstituents that shows anti MRSA activity. The MRSA strains can spread easily in hospitals from colonized or from the infected persons where the colonized ones are generally asymptomatic whereas they are being a potential reservoir of infections acquired by patients.

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