DISCUSSION

Infections by gram positive organisms are an increasing epidemiologic problem worldwide; especially staphylococcal infections produced by *Staphylococcus aureus* are most prominent in the hospital environment. The rate of MRSA represents 11% of all isolates of *Staphylococcus aureus* in the U.S with 32% of all Hospitals and 12% of all Nursing Homes reporting isolation of this organism (Dar et al., 2006). Vancomycin and teicoplanin are both large polar molecules, as they cannot penetrate the lipid membrane gram negative bacteria they are inactive against these organisms. These two are widely used in the treatment of infections caused by gram positive organisms. Meta analysis of the number of adverse events occurring in each treatment group showed significant fewer reports of adverse events in patients receiving Teicoplanin 13.9% than those receiving vancomycin 21.9%.

Methicillin-resistant *Staphylococcus aureus* (MRSA) isolates came into existence soon after the introduction of methicillin. Historically, MRSA isolates have been associated with nosocomial infections and rapidly developed resistance to multiple drug classes (Schaberg et al, 1991). However, in recent years, different strains with unique phenotypes have
emerged in the community, and the reservoir of community-associated MRSA is rapidly expanding.

Methicillin-resistant *Staphylococcus aureus* is a pathogen that is associated with serious infections that pose a significant risk of morbidity and mortality because of their multidrug resistant nature. Until recently, therapeutic options were limited to vancomycin, making the use of this drug widespread. Unfortunately, the continued application of this drug has led to the emergence of glycopeptide intermediate susceptible *Staphylococcus aureus* (GISA). GISA strains have demonstrated thickened or aggregated cell walls, an increase in penicillin binding proteins and greater autolytic activity. At present, the overall number of reported cases of GISA is relatively low.

Multidrug resistance is common in HA-MRSA. It is worrisome that, VISA have been isolated with an increased incidence since 2002. Multidrug-resistant strains of both VISA and VRSA have been detected, suggesting that the efficacy of antimicrobial agents for systemic infections such as bacteremia, endocarditis, and osteomyelitis may soon be significantly compromised.

Available automated methods, such as Vitek (bioMerieux) and Microscan (Dade Behring), do not identify all known strains of VRSA
adequately and should not be used for the routine detection of hVISA and VISA. A vancomycin agar screening plate should be used. Existing commercially available screening plates still contain a vancomycin concentration of 6 μg / mL. In addition, routine screening for glycopeptide resistance must be done when MRSA strains are isolated, to detect such strains early and to prevent outbreaks. In all cases, at the very least, a vancomycin agar screening test with a more appropriate vancomycin concentration (to be determined, but < 6 μg/mL) should be used. A better approach, in countries with the financial capability, is routine testing of all MRSA strains with an overnight vancomycin Etest strip (AB BIODISK), followed, if necessary, by a macro E-test for all isolates with Vancomycin MICs of 1–2 μg / mL isolated from patients with *Staphylococcus aureus* infections not responding to vancomycin therapy. A macro E-test comparing vancomycin and teicoplanin can easily differentiate between VISA and hVISA. Vancomycin is susceptible when both MICs are low, hVISA when the vancomycin MIC is low but the teicoplanin MIC is high, and VISA when both MICs are high. It has been reported that teicoplanin susceptibility in MRSA is lost before vancomycin susceptibility. The lower baseline activity of teicoplanin for MRSA, compared with that of vancomycin, may result in easier emergence of resistance to teicoplanin.
To improve the detection of vancomycin or glycopeptide resistance in MRSA, it is very important to consider the testing method. The E-test may offer the best alternative method.

**Morphological changes of VISA/GISA**

Staphylococcus bacteria are classified as VISA or VRSA based on laboratory tests. Laboratories perform tests to determine if staphylococcus bacteria are resistant to antimicrobial agents that might be used for treatment of infections. For vancomycin and other antimicrobial agents, laboratories determine how much of the agent it requires to inhibit the growth of the organism in a test tube.

**Staphylococcus aureus: Development of High-Level vancomycin Resistance**

MRSA is a common cause of infection among hospitalized patients. vancomycin is the typical treatment for these infections, but over the last decade there has been increasing concern about the development of MRSA strains with reduced susceptibility to vancomycin. The first report of an MRSA strain with reduced susceptibility to vancomycin (MIC 8 ug/mL) reported as a vancomycin Intermediate *Staphylococcus aureus* (VISA) appeared in Japan in 1997.
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The sheer volume of antibiotics prescribed is the major factor in increasing rates of bacterial resistance rather than compliance with antibiotics (Abigail et al., 2005). A single dose of antibiotics leads, to a greater risk of resistant organisms to that antibiotic in the person for up to a year. Inappropriate prescribing of antibiotics has been attributed to a number of causes, including people who insist on antibiotics, physicians who simply prescribe them as they feel they do not have time to explain why they are not necessary, and physicians who do not know when to prescribe antibiotics or else are overly cautious for medical legal reasons.

Antibiotic resistance has been shown to increase with duration of treatment; therefore, as long as a clinically effective lower limit is observed the use by the medical community of shorter courses of antibiotics is likely to decrease rates of resistance, reduce cost, and have better outcomes (Costelloe, 2010). In some situations a short course is inferior to a long course (Perez-Gorricho & Ripoll, 2003). One study found that with one antibiotic a short course was more effective, but with a different antibiotic, a longer course was more effective (Keren & Chan, 2002).

Advice to always complete a course of antibiotics is not based on strong evidence, and some researchers discourage the use of the
prescription label “Finish all this medication unless otherwise directed by prescriber”. Often, antibiotics can be safely stopped 72 hours after symptoms resolve.

A large number of people do not finish a course of antibiotics primarily because they feel better (varying from 10% to 44%, depending on the country). Compliance with once-daily antibiotics is better than with twice-daily antibiotics (Pechère, 2007). Patients taking less than the required dosage or failing to take their doses within the prescribed timing results in decreased concentration of antibiotics in the bloodstream and tissues, and in turn, exposure of bacteria to suboptimal antibiotic concentrations increases the frequency of antibiotic resistant organisms.

Antibiotic-tolerant states may depend on physiological adaptations without direct connections to antibiotic target activity or to drug uptake, efflux, or inactivation. Poor hand hygiene by hospital staff has been associated with the spread of resistant organisms (Thomas et al., 1998) and an increase in hand washing compliance results in decreased rates of these organisms.

The improper use of antibiotics and therapeutic treatments can often be attributed to the presence of structural violence in particular regions. Socioeconomic factors such as race and poverty affect the accessibility
and adherence to drug therapy. Antibiotic resistance can also be introduced artificially into a microorganism through laboratory protocols, sometimes used as a selectable marker to examine the mechanisms of gene transfer or to identify individuals that absorbed a piece of DNA that included the resistance gene and another gene of interest. A recent study demonstrated that the extent of horizontal gene transfer among *Staphylococcus* is much greater than previously expected and encompasses genes with functions beyond antibiotic resistance and virulence, and beyond genes residing within the mobile genetic elements (Li & Nikadio, 2009).

For a long time it has been thought that for a microorganism to become resistant to an antibiotic, it must be in a large population. However, recent findings show that there is no necessity of large populations of bacteria for the appearance of antibiotic resistance. These mutations confer the bacteria emergence of antibiotic resistance.

A common misconception is that a person can become resistant to certain antibiotics. It is a strain of microorganism that can become resistant, not a person’s body. Presently, MRSA are the common organisms associated with hospital acquired infections worldwide. Prevalence of MRSA varies markedly by institutions. The prevalence of
MRSA in hospital was determined to be 33%, generally conforming to the average Indian data (Anupurba et al., 2003). Antibiotic pressure is known to select mutants that can survive the adverse conditions. In a hospital, constant use of antibiotics results in survival and spread of MRSA, extended spectrum beta- lactamase producers and multidrug resistant enterococci. By virtue of changing the penicillin binding sites PBP, MRSA survives in the presence of almost all beta lactam antibiotics, the mainstay of treating most infections in modern hospital practice. Major factor in the mechanism of resistance to beta-lactams in MRSA is known to be the alteration at the site of penicillin binding protein, PBP2' or PBP2 resulting in low affinity for the beta-lactams (Fang & Hedin, 2003). Prior antibiotic treatment primes the organism to develop resistance. Ten percent of patients who were admitted elsewhere for treatment and subsequently referred to this hospital were found to be infected with MRSA at the time of admission. Hospital to hospital transmission may also be responsible for increasing the load of MRSA in referral hospitals.

Resistance to most beta lactam antibiotics and some of the other classes of antibiotics poses a problem in treating an infection with MRSA (Krishna et al., 2002). Vancomycin, a glycopeptide antibiotic has been the drug of choice for treatment of serious staphylococcal infections for
decades with no resistance emerging until the late 1990s. MRSA with reduced susceptibility to vancomycin was first reported in 1997 in Japan. Full blown resistance to this antibiotic has been reported from US. Resistant strains responsible in serious infections underscore the need for the development of alternate antimicrobial agents to vancomycin. Non compliance is often a problem among poor patients due to the high cost of a full course of vancomycin or other glycopeptides.

Linezolid was found to be as effective as vancomycin in the treatment of nosocomial pneumonias as well as skin and soft tissue infections. Linezolid appears to be one of the few available antimicrobial agents with proven activity against multi resistant *Staphylococcus aureus* including strains with reduced susceptibility to glycopeptides. In the present study all isolates were sensitive to linezolid. All the patients receiving linezolid had full recovery as shown by negative follow up cultures. Linezolid has been approved for human use following *in vitro* studies to demonstrate antimicrobial activity against gram positive pathogens such as *Staphylococcus aureus* the antibiotic showed a good *in vitro* activity in the present study.

Minimum inhibitory concentration and high cost of treatment is one of the major causes of non compliance by patients. In a developing country
like India, majority of the patients are unable to afford a full course. This results in a vicious cycle of inadequate treatment leading to emergence of further resistance and spread of MRSA. Therefore, it is imperative to explore alternate effective antibiotic regimen to eradicate MRSA from the hospital and avoid spread in the community. In conclusion, the present study identified prior antibiotic use and admission to intensive care units, as some of the risk factors associated with infections due to MRSA. Emergency admissions had a higher chance of early isolation. Clindamycin showed very good *in vitro* activity. Its use may be explored cautiously. Effective prevention and control of infections due to MRSA depends on practice of infection control measures such as hand washing. Minimizing risk factors and attention to alternate cost effective combination therapy may ease the problem of management of infections with MRSA.

**Teicoplanin resistance**

Teicoplanin and vancomycin belong to the glycopeptide class of antibiotics. Both exert antimicrobial activity by binding to the D-alanyl-D-alanine residue of murein monomer. Therefore, a common resistance mechanism for the two antibiotics is to be expected. In fact, all the VRSA strains analyzed, possess teicoplanin resistance (defined by MIC 8 mg/L). Cell-wall thickness also contributes to teicoplanin resistance as expressed
by the VRSA strains (MIC 8–32 mg/L) and resistance decreases when cell-wall thickness decreases. However, about half of the vancomycin-susceptible revertants of VRSA strains still maintain intermediate levels of teicoplanin resistance (MIC 8 or 16 mg/L). This finding suggests that there may be other mechanisms than cell-wall thickness for teicoplanin resistance. Historically, *Staphylococcus aureus* acquired teicoplanin resistance before it acquired vancomycin resistance. There are quite a few MRSA strains that are resistant to teicoplanin but are still “susceptible” to vancomycin as judged by MIC values.

However, acquisition of teicoplanin resistance is frequently accompanied by a small increase in vancomycin resistance in fact, hetero-VRSA strains belong to this category of strains Shale and colleagues demonstrated that PBP2 is overproduced in a teicoplanin-resistant *Staphylococcus aureus* mutant strain (MIC 16 mg/L) compared with its parent clinical strain. Over-production of PBP2 is also observed in Mu50 and the hetero-VRSA strain Mu3—both are resistant to teicoplanin. The experimental over expression of PBP2 in a VSSA strain causes the vancomycin MIC to increase by 1 mg/L (from 1 to 2 mg/L), whereas that of teicoplanin increased significantly from 2 to 8 mg/L. In agreement with its marginal contribution to vancomycin resistance, over-expressed PBP2
alone does not lead to cell wall thickening. On the other hand, it increases the rate of cross-linking of cell-wall peptidoglycan. This finding highlights again the difference between the two glycopeptides. It may be that teicoplanin is more prone to inhibiting transpeptidation than vancomycin, and vancomycin more inclined to inhibit transglycosylation.

The importance is stressed of two factors that are susceptible to modification in normal clinical practice the unnecessary use of antibiotics that can give rise to the appearance of multi resistant strains, and limiting the propagation of such strains (by means of the adoption of standard precautions and especially hand washing).

VISA isolates reported to date have a vancomycin MIC of 8 mg/L, and were isolated from patients with underlying diseases whose long-term vancomycin treatment apparently failed. Since many VISA isolates also have been resistant to teicoplanin, the term glycopeptide-intermediate \textit{Staphylococcus aureus} (GISA) is more appropriate. The frequency of GISA isolates appears to be extremely low to date, only 10 GISA infections have been reported worldwide. However, heterogeneous resistance to glycopeptides (h-GISA) have been reported in Japan, Europe and Thailand. These h-GISA strains showed vancomycin MICs ranging from 1 to 4 mg/L, but had subpopulations that could grow on agar plates.
containing 4-8 mg/L, which may represent the first step in the development of GISA strains. Currently, there are no recommended therapy guidelines for GISA infections, although in recent studies, several new drugs have shown promising activity against GISA strains. In addition, synergy between glycopeptides and beta-lactams against GISA strains were observed in some *in vivo* and *in vitro* studies. Specific MRSA/GISA control programs, rational antibiotic policies, including the reduction of glycopeptide use, and rapid laboratory detection of GISA and h-GISA strains are the key measures in preventing the spread of these strains.

Virtually every antibiotic introduced into clinical practice has encountered resistance at one level or other. *Staphylococcus aureus* is one such pathogen that has shown disconcerting propensity to develop resistance to a number of antimicrobials and MRSA is one such group that has been a matter of concern since late 1970s. Vancomycin, a glycopeptide, is currently the main antimicrobial available to treat infections with these MRSA.

Widespread use of vancomycin to treat infections caused by MRSA has been reported to result in the emergence of low level resistance. In very few instances only VISA are a definite entity now. But the large scale development and subsequent spread of resistance to vancomycin is
perceived as a fearsome threat to the already challenging therapy of MRSA.

Systems, which used to perform susceptibility testing, do not provide a precise vancomycin MIC. Therefore laboratories are using alternative methods for testing vancomycin in selected cases (Hsu et al., 2008). The E-test method is an alternative and feasible option for vancomycin testing since it is easy to perform and cost-effective for testing only one drug for one strain. Interpretation of results is also easy. We recommend using E-test as a routine test for determining MIC because of the above mentioned reasons. Agar dilution test should be done on all those strains showing higher MIC by E-test. Routine use of agar dilution is cumbersome and labor intensive.

**Strategies to counter VRSA infection**

The nature of the resistance mechanism of VRSA—production and accumulation of excess amounts of cell-wall peptidoglycan—indicates that VRSA would not be prevalent in an environment where the glycopeptide selective pressure is not strong. If a hospital reduces the consumption of glycopeptides, VRSA should not prevail in the hospital.

However, this action does not solve the problem completely, because hetero-VRSA may be capable of dissemination without glycopeptide
pressure. Therefore, it is necessary to expand antibiotic prescription policy to include beta-lactam antibiotics as well. If we reduce consumption of broadspectrum cephalosporin (which are ineffective against MRSA), and this measure combined with effective infection control, the number of MRSA in the hospital would decrease according to a mathematical model developed by Lipsitch et al., (2001). Reducing the total number of MRSA is the most effective measure for preventing emergence of VRSA and hetero-VRSA. Recently, successful reduction of MRSA was achieved in a Japanese hospital by cutting the total use of broad-spectrum cephalosporins by half without compromising infection outcome. It may also be possible to reduce the selection of vancomycin resistance in MRSA isolates in the hospital by substituting cephalosporins and carbapenems with penicillin that have a relatively strong anti-MRSA activity among beta-lactam antibiotics.

A certain group of Staphylococcus aureus, designated hetero-VRSA, frequently generate VRSA upon exposure to vancomycin, and are associated with infections that are potentially refractory to vancomycin therapy. Presence of hetero-VRSA may be an important indicator of the insidious decline of the clinical effectiveness of vancomycin in the hospitals. Vancomycin resistance is acquired by mutation and thickening of cell wall
due to accumulation of excess amounts of peptidoglycan. This seems to be a common resistance mechanism for all VRSA strains isolated in the world so far.

Recent emergence of Vancomycin resistance in methicillin-resistant \textit{Staphylococcus aureus} (VRSA) has posed a new threat to hospital infection control and antibiotic chemotherapy (Hiramatsu, 2001). It summarizes the history of emergence of glycopeptide resistance in staphylococci and considers the mechanism of resistance in these organisms.

Prolonged therapy of MRSA infections with teicoplanin has been associated with development of resistance in earlier reports. Teicoplanin resistance in MRSA has been reported in ICUs that use this glycopeptide as a first-line antibiotic.

The glycopeptides, vancomycin and, to a lesser extent, teicoplanin, are the mainstay of therapy for infections caused by Methicillin Resistant \textit{Staphylococcus aureus} (MRSA), (Peter \textit{et al.}, 2001) and currently up to half of all \textit{Staphylococcus aureus} strains isolated in hospitals in Australia are MRSA. Despite substantial glycopeptide use over many years, the emergence of MRSA strains with reduced susceptibility to vancomycin and teicoplanin has been reported only recently. Subsequently, MRSA strains
have been reported that contain limited subpopulations with intermediate resistance to glycopeptides, while most of the population remains glycopeptide-susceptible. These are termed heteroresistant vancomycin-intermediate \textit{Staphylococcus aureus} (hVISA).

The identification of hVISA may be the beginning of a new phase in the emergence of antibiotic resistance in Australia, when the glycopeptides vancomycin and teicoplanin will no longer be effective in some cases of MRSA infection. This raises challenges for clinical management, laboratory detection and infection control. Furthermore, while two recently available agents, linezolid and quinupristin-dalfopristin, appear active against hVISA, VISA, MRSA.

Substantial evidence was provided that acquisition of teicoplanin resistance by \textit{Staphylococcus aureus} may be linked with multiple changes in the expression and regulation of virulence genes. In line with a recent report showing that a majority of GISA isolates were recovered from device-associated infections, the link between emergence of Teicoplanin resistance in \textit{Staphylococcus aureus} and increased attachment to fibronectin may be of significant clinical relevance if it could be extended to clinical GISA strains. In fact, fibronectin-binding proteins play a prominent
role in *Staphylococcus aureus* attachment and colonization of host tissue and implanted biomaterials.

Both the terms glycopeptide-intermediate *Staphylococcus aureus* (GISA) and vancomycin-intermediate *Staphylococcus aureus* (VISA) have been used in the literature and in essence are interchangeable. However, it is clear that reduced teicoplanin susceptibility can be present in *Staphylococcus aureus* without a clearly demonstrated reduction in vancomycin susceptibility whereas generally, VISA strains have demonstrated reduced teicoplanin susceptibility. Because the majority of *in vitro* susceptibility testing uses vancomycin, and much of the literature uses the term vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous VISA (hVISA).

**Understanding vancomycin Resistance**

To understand the mechanisms and potential impacts of vancomycin resistance in *Staphylococcus aureus*, a clear understanding of the organism's cell wall is required. The staphylococcal cell wall is a dynamic structure important for maintaining cell integrity and critical in host-pathogen interactions (Tomasz, 2006). The outermost surface of *Staphylococcus aureus* is usually covered by a polysaccharide capsule. Under the capsule lies the cell wall, a structure composed of highly cross-
linked peptidoglycan (PG) (a complex structure composed of sugars and amino acids, also called murein), teichoic acids, and cell wall-associated proteins (Dmitriev, 2004). The peptidoglycan is composed of glycan chains made up of the alternating amino sugars N-acetyl glucosamine and N-acetyl muramic acid. Stem pentapeptides (l-Ala-d-iso-Gln-l-Lys-d-Ala-d-Ala) are attached to the carboxyl group of each N-acetyl muramic acid, and inter peptide bridges (pentaglycines, made up of glycine residues) connect the lysine component of one stem peptide to the penultimate d-alanine of a neighboring stem peptide. Teichoic acid chains are attached to the 6-hydroxyl groups of some of the N-acetyl muramic acid residues of the glycan chains and, together with the peptidoglycan, form a multi-layered network that surrounds the *Staphylococcus aureus* cell. The stress-bearing murein therefore represents a continuous macromolecule encasing the sacculus. Typically, the degree of murein cross-linking in the *Staphylococcus aureus* cell wall is high, with bridged peptides as a ratio of all peptide ends in the order of 80 to 90% (Snowden, 1989). The peptidoglycan composition from different *Staphylococcus aureus* strains is highly conserved, with almost identical high-performance liquid chromatography (HPLC) muropeptide patterns across strains, suggesting that the composition is species specific.
The consequence of this modification includes cell wall thickening, decreased autolysis, reduced protein A production, increased capsule expression, increased d-alanylation of teichoic acids, and reduced agr activity.

Resistance arises intrinsically upon glycopeptide exposure, as the result of multiple mutations and/or alterations in gene expression. Several of the clinical and laboratory GISA strains described share phenotypic similarities (Cui et al., 2006). Most commonly a modification of the cell wall, reducing the amount of glycopeptide able to reach its target at the cell membrane. Common GISA features include cell wall thickening, decreased peptidoglycan cross-linking, decreased growth rate and hemolysis, alterations in rates of autolysis, and changes in the structure and/or abundance of cell wall teichoic acids. However, there is still little known about the genetic basis of this phenotype, and there is no universal genetic marker typical for all GISA isolates.

Teicoplanin and vancomycin are the drugs of choice against multidrug-resistant methicillin-resistant *Staphylococcus aureus*. Their antibacterial activity is based on the ability to bind the terminal d-alanyl-d-alanine present in the lipid-II-linked peptidoglycan precursor and in peptidoglycan intermediates, thereby inhibiting transglycosylation and
transpeptidation of the cell wall. Though both drugs interact with the same target, teicoplanin anchors to the membrane while vancomycin forms dimers to increase its activity. Even though teicoplanin is more active than vancomycin against staphylococci (Felmingham, 1998) resistance to teicoplanin is more easily acquired than resistance to vancomycin. Teicoplanin resistance is believed to precede vancomycin resistance reviewed in reference. In clinical isolates of *Staphylococcus aureus*, teicoplanin resistance was found to emerge during extended teicoplanin treatment (Kaatz, 1990) suggesting an in vivo selection for resistant mutants. In contrast to the van gene-mediated glycopeptide resistance in enterococci, resistance in *Staphylococcus aureus* is not due to acquisition of foreign elements but formed endogenously. Analogously, teicoplanin-resistant mutants can be obtained in vitro by step selection for growth on increasing concentrations of the drug. Such, in vitro-selected teicoplanin-resistant mutants may have characteristics similar to those of clinical teicoplanin-resistant isolates, allowing their use to study the genes involved in the resistance mechanism. Except for the work of Shlaes (Shlaes, 1993) who identified a site in the Smal-I fragment of the *Staphylococcus aureus* chromosome responsible for increase in a 35-kDa protein and PBP 2
production in teicoplanin-resistant *Staphylococcus aureus*, few genetic studies of teicoplanin resistance have been done.

**Clinical impact of hVISA, VISA and elevated Vancomycin MIC**

The spectrum of clinical disease caused by hVISA and VISA is similar to that caused by VSSA, but the prevalence and clinical impact are difficult to determine due to the lack of a standardized definition and absence of controlled prospective studies. High-inoculum infections such as bacteremia, endocarditis and osteomyelitis (Maor, 2009) and persistent bacteremia (Howden, 2006) have been associated with vancomycin heteroresistance, and this may lead to vancomycin treatment failure or other complications. However, it is difficult to determine whether hVISA is the cause or corollary of treatment failure in some studies, especially if it is not clear when the hVISA or VISA isolate was detected in the course of the infection. Interestingly, one study noted reduced rates of shock in patients with hetero resistant infections compared with VSSA infections possibly demonstrating a clinical correlate of the attenuated virulence noted in animal models of VISA infection.

Interestingly, pooled data from a recent meta-analysis demonstrated similar mortality rates for VSSA and hVISA infections; however, treatment failure was more common in the hVISA group (Van & Paterson, 2011). Clinical factors associated with an elevated vancomycin MIC are similar to those associated with the development of hVISA and include prior
vancomycin exposure prior methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, and increased patient age.

The underlying mechanism by which an elevated vancomycin MIC in VSSA causes inferior outcomes has not yet been elucidated. It has been suggested that vancomycin treatment be avoided in these situations, as it is presumed that the continuum of changes that lead to reduced vancomycin susceptibility and hVISA is implicated in the development of resistance. In addition, reduced vancomycin bactericidal activity in VSSA isolates with an elevated vancomycin MIC *in vitro* has been previously noted.

As we obtained three teicoplanin resistant blood isolates with a greater MIC of 8 twice and 12 ug. All the three teicoplanin resistant blood isolates were sensitive to vancomycin and clindamycin. One isolate was resistant to erythromycin. So clindamycin was administered twice daily for five days for the patient with respiratory infection and vancomycin was administered for the other two patients who suffered from bacteraemia.

While the clinical significance and the need to detect VRSA is without question, and probably so for GISA this is not the case for hGISA, although there have been several reports of glycopeptide treatment failure associated with hGISA (Timothy & Walsh, 2002). One report concluded that a significant risk for vancomycin treatment failure in MRSA bacteremia begins to emerge with increasing vancomycin MICs (>0.5 mg/L) well within the susceptible range. It seems likely that reduced glycopeptide
susceptibility in hGISA may be significant in serious infections. Several studies have shown that GISA can be derived from hGISA by selection with glycopeptides \textit{in vitro}, suggesting that hGISA may be precursors of GISA.

Linezolid have also been used for treatment of MRSA with good outcomes. Nearly 100% is absorbed by the gastro intestinal tract. Compared with glycopeptides linezolid achieves higher lung epithelial lining fluid concentration which may correlate with improved efficacy in the treatment of nosocomial pneumonia. Linezolid is relatively a safe drug when administered for short periods. It can be used in patients of all ages and in people with liver disease or poor kidney function. If used for longer periods it may cause peripheral neuropathy, bone marrow suppression and low platelet count, particularly used for more than two weeks. Because of its excellent bio availability, even though it is expensive, the option of oral treatment is very appealing and can reduce hospital length of stay.

Vancomycin is often recommended as a standard treatment for systemic infections as parenteral agent. Efficacy of vancomycin treatment in endocarditis gives a slow clinical response preference of \( \beta \)-lactams is also favored from a microbial ecology standard point to reduce selective pressure for vancomycin resistant gram positive flora. Vancomycin is one of the drugs of choice for staphylococcal pneumonia in American Thoracic Society (ATS) and the infectious diseases society of American guidelines.
Clindamycin is more widely used to treat staphylococcal infections because of its good penetrations into bone. It is sometimes used to treat osteomyelitis such as diabetic foot.

Daptomycin is a cyclic lipopeptide which achieves bactericidal activity against gram positive bacteria by inserting into cell membrane and causing membrane depolarization. It has been shown to be non-inferior to β-lactams and vancomycin. Clinicians should confirm daptomycin susceptibility before switching to this agent in patients in failing vancomycin therapy.

Tigecycline is a glycyl cycline and has a broad spectrum of activity. It is used in the treatment of adults with complex skin and soft tissue infections. It is also administered in complex intra abdominal infections.
SUMMARY

The present study is an effort in understanding the importance of glycopeptide resistance in Methicillin Resistant Staphylococcus aureus (MRSA). Staphylococcus aureus has long been recognized as a major pathogen of hospital acquired infections. Over the last decade Methicillin resistant Staphylococcus aureus strains have become endemic in hospitals worldwide. In addition, it is now incipient community pathogen in many geographical regions. MRSA is important because, in addition to being methicillin resistant, most strains are also resistant to other β – lactam antibiotic, with the exception of glycopeptide antibiotics.

The samples include pus, pus swabs, blood cultures, central line tip, Endo tracheal secretion ascitic fluid, pleural fluids. All these samples were initially screened for MRSA following British Society for Antimicrobial Chemotherapy guidelines (BSAC, 2011). Various isolates of MRSA are taken. All the samples which are screened for MRSA are found to be coagulase positive. The steps involved in processing of the sample included inoculation, identification, isolation, screening, observing antimicrobial susceptibility by disc diffusion method and finally determining the Minimum inhibitory concentration of glycopeptides by E-test method.
Minimum inhibitory concentration (MIC) of the glycopeptides namely vancomycin and teicoplanin are noted. Of the samples processed all isolates were found to be vancomycin susceptible showing that there is no resistance observed among the most commonly used glycopeptide namely vancomycin. Three isolates were found to be teicoplanin resistant following BSAC guidelines 2011.