

Challenges in the Laboratory Diagnosis and Clinical Management of Heteroresistant Vancomycin *Staphylococcus aureus* (hVISA)

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Abstract

MRSA is a public health threat and significant cause of health care-associated and community-associated infections. Vancomycin is considered as gold standard in treating life-threatening infections. Recently, reduced vancomycin susceptibility has been reported across the world. However, infection with *S. aureus* resistant to vancomycin is clinically rare and less relevant in causing infections. The clinical failure of vancomycin therapy is being increasingly reported with vancomycin intermediate *S. aureus* (VISA) and hetero-resistant vancomycin intermediate *S. aureus* (hVISA). The therapeutic option in treating hVISA and VISA remains uncertain. Extensive use of vancomycin over a period of time leads to generation of selective pressure and emergence of resistance. In addition, vancomycin has low tissue penetration, slow bactericidal activity and risk of nephrotoxicity. Although, phenotypic feature of VISA and hVISA were well known, their genetic basis remains unknown. VISA and hVISA is generated by the accumulation of mutation leads to thickening of cell wall. Trapping of vancomycin molecule occurs due to the presence of false targets D-ala D-ala residues in the cell wall, before reaching its target site in cytoplasmic membrane. Despite, it is difficult to detect hVISA using standard susceptibility testing methods. Treatment failure is common among patients with high bacterial load infections. Treating of patients with hVISA/VISA infections is of great challenge for clinicians.

Introduction

Vancomycin has remained the mainstay for the treatment of MRSA infections in the past four decades and the emergence of resistance to this drug has been very slow. Vancomycin, a glycopeptide antibiotic, was introduced into clinical practice in 1958 to treat life threatening infections caused by Gram positive organisms. It acts by inhibiting cell wall synthesis by binding to cell wall precursors such as D-ala-D-ala residues. The molecule is large and rigid and hence its binding to the residues causes steric hindrance which results in inefficient cell wall synthesis [1]. Overuse of vancomycin has led to the development of a selective pressure over time leading to emergence of reduced vancomycin susceptibility among *S. aureus* strains. Since the repertoire of drugs available for treating MRSA, not responding to vancomycin is limited, emergence of MRSA with reduced susceptibility to vancomycin is dangerous and worrisome. This review will summarize the current knowledge on mechanism of resistance, clinical impact and laboratory diagnosis of hVISA

Heteroresistant Vancomycin Intermediate *S. aureus* (hVISA)

There is no precise definition for heteroresistant vancomycin intermediate *S. aureus* (hVISA). As per CLSI guidelines, hVISA has been found to reside within the susceptible range of MIC (≤ 2 $\mu\text{g/ml}$) where a notable subpopulation of resistant cells presents approximately at a frequency of 1 in 10^5 cells to 10^6 cells [2]. If the proportion of MRSA in a population expressing vancomycin resistance is sufficiently high, it can be detected with the standard low inocula of susceptibility testing as non-susceptible. However, hVISA

subpopulations occur at frequency far below the threshold of standard inoculum and misidentified as susceptible with standard susceptibility testing. Moreover their varying levels of resistance and extremely unstable phenotypic expressions render their detection more complicated [3].

hVISA and VISA share the same mechanism of resistance whereby increased cell wall thickness and high number of D-ala-D-ala residues cause a trapping of the large vancomycin molecules [4] (Table 1). The hVISA is considered as the precursor stage of VISA wherein selection pressure created by sub-therapeutic levels of vancomycin therapy can aid the selective growth of these resistant subpopulations. Prolonged therapy with vancomycin eventually leads to a uniform population of strains expressing VISA.

Molecular Determinants of hVISA and VISA

Vancomycin binds with pseudotarget or false target (D-ala-D-ala residues) with high affinity cell wall peptidoglycan layer. However, the binding doesn't affect the cell viability. Because the vital target is missed by vancomycin [5,6]. Thus, vancomycin hardly penetrates the cell wall into cytoplasmic membrane. Studies have reported the gene expression and mutation in regulatory genes is crucial for the cause of cell wall thickening and alteration of metabolism. The present knowledge on specific genetic determinants of hVISA and VISA was inadequate.

Currently, understood emergence of hVISA and VISA was reported to occur due to:

- mutation in the regulatory genes, this includes; *vraSR* two component regulatory systems (TCRS) and *walkR* two component regulatory systems (Figure 1A) and
- *rpoB* gene mutation (Figure 1B).

Characteristics	hVISA	VISA	VRSA
MIC	1-2 µg/ml	4-8 µg/ml	≥ 16 µg/ml
Mechanism of resistance	Cell wall thickening and hyperproduction of glycopeptide binding targets	Cell wall thickening and hyperproduction of glycopeptide binding targets.	Substitution of D-Ala-D-Ala with D-Ala-D-Lac
Gene encoding for resistance	Endogenous resistance-Chromosomal mutation	Endogenous resistance-Chromosomal mutation	Van A
Recommended methods for detection in CLSI guidelines	-	Vancomycin MIC: E-test, Microbroth dilution method	Vancomycin MIC: E-test, Microbroth dilution method
Recommended methods for detection in EUCAST guidelines	Screening methods (hVISA, VISA and VRSA): Macro E-test, Glycopeptide resistance detection test and Teicoplanin screening agar. Confirmatory testing for hVISA/VISA: Population analysis profile-Gold standard		

Table 1: Characteristics of hVISA, VISA and VRSA.

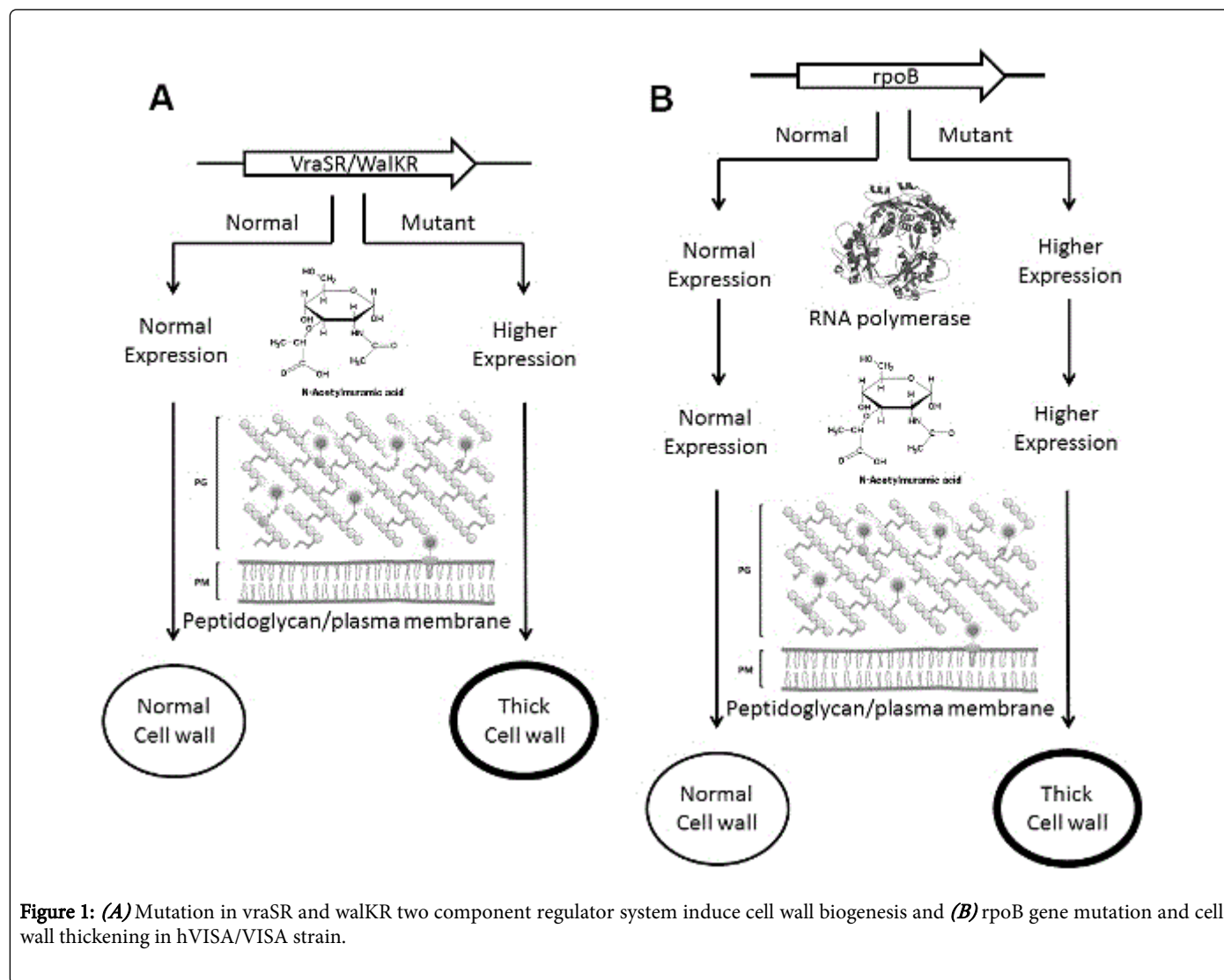


Figure 1: (A) Mutation in *vraSR* and *walkR* two component regulator system induce cell wall biogenesis and (B) *rpoB* gene mutation and cell wall thickening in hVISA/VISA strain.

Mutation in either of *vraS* (sensor kinase gene) and *vraR* (response regulator gene) leads to constitutive activation and over expression of *vraSR* TCRS. This two component regulatory system (*vraSR*) is a part operon system *vraU-vraT-vraS-vraR* and is frequently get mutated in hVISA and VISA clinical strains [7].

In addition, increases the expression of genes encoding enzymes *murZ*, *pbp2*, *sgtB*, *tarA*, *fmtA* and *lcpC* and are involved in cell wall synthesis [8]. The *vraSR* function is determined by *vraT/YvqF*. A mutation in *vraT* (Y220C), activate both *vraS* and *vraR* and promote upregulation of cell wall biosynthesis. This mutation contributes to the raised level of methicillin and vancomycin resistance. In addition, another variant mutation in *vraT* (T125I) increases the resistance to both vancomycin and imipenem [9]. Interestingly, up-regulation of two component regulatory system (*vraSR*) consisting of sensor kinase (*vraS*) and response regulator (*vraR*) are induced not only with vancomycin but also found with β -lactam antibiotics [10]. *Kato et al.*, has performed genetic analysis for the detection of known gene mutation in clinical VISA strains. In this study, 14 (42.4%) of strains were identified with mutation in either one of the *vraT/YvqF*, *vraS* and *vraR* genes in the four-membered operon system [11].

In *walKR* TCRS, *walK* is a sensor histidine kinase and *walR* response regulator. In addition, TCRS regulate the expression of autolysins. A mutation identified in *walK* gene, not only increases the vancomycin resistance but also reduce the autolysis of hVISA and VISA strains [12]. Interestingly, among VISA strains *rpoB* gene mutation was common. The *rpoB* gene mutation greatly influences the overall transcription of the cell metabolism [13].

Remarkably, mutation in the regulatory gene *graR* coupled with *rpoB* mutation translates low-level vancomycin resistant hVISA to high level VISA strains. However, additional studies are essential to establish this association and conversion of hVISA to VISA further [14].

Clinical Significance of Heterogeneous Resistance to Vancomycin in *S. aureus*

Though the spectrum of infections caused by hVISA/VISA is similar to that of VSSA, the clinical importance of infections remains controversial. It is uncertain whether the hVISA and VISA are more

virulent than VSSA isolates and whether their unpredictable level of resistance is responsible for treatment failure [15]. Literature review favours a more favourable outcome for skin and soft tissue infections than nosocomial pneumonia, meningitis, osteomyelitis and endocarditis. It is very difficult to determine the reason for treatment failure if hVISA was detected during the course of infection [16].

In 2003, *Moore et al.* were able to provide experimental data demonstrated that hVISA was responsible for vancomycin treatment failure in an endocarditis patient. In the study, both pre-treatment and relapse MRSA isolates had MIC of <2 mg /ml for vancomycin but the PAP analysis proved that relapse isolate has subpopulations of hVISA. Further testing with rabbit model of endocarditis also proved that the heterogeneous resistance of relapse hVISA isolate was responsible for treatment failure [17].

Even though earlier studies have failed to conclusively identify the relationship between hVISA and poor clinical outcomes, a recent meta-analysis study by *Van Hal et al.* have reported a 2.37 fold increased risk of vancomycin treatment failure in patients with hVISA than VSSA, although the overall mortality rates for hVISA and VSSA infections was similar [18].

The increasing reports of vancomycin therapy failure with higher MICs and the increasing reports of hVISA isolates prompted the CLSI to revise the breakpoints for vancomycin MIC for *S. aureus* in 2006. The rationale behind this move was that lower susceptible ranges was more likely to exclude the hVISA strains occurring more frequently at higher MICs from the susceptible ranges and hence reducing the possibilities for therapeutic failure. The revisions of the MICs are given in Table 2.

Clinical Markers of hVISA/VISA Infections

Clinical outcome of hVISA infection varies with the infection site, severity of infection and the presence of any foreign body. Potential markers of hVISA infection were found to be the presence of high bacterial load such as with endocarditis and pneumonia, persistent fever and bacteraemia, worsening of signs of infections after commencement of vancomycin therapy, and presence of prosthetic devices such as orthopedic implants, artificial valves, and pacemakers [19,20].

Vancomycin interpretation	Phenotypes	Broth Microdilution method (Reference method recommended by CLSI, EUCAST, BSAC, etc)		
		CLSI interpretation prior to 2006 (in $\mu\text{g/ml}$)	CLSI interpretation after 2006 (in $\mu\text{g/ml}$)	EUCAST interpretation (in $\mu\text{g/ml}$)
Susceptible	VSSA	≤ 4	≤ 2	≤ 2
*Heteroresistant	*hVISA	-	-	-
Intermediate	VISA	8-16	4-8	Excluded from the definition
Resistant	VRSA	≥ 32	≥ 16	>2

*Heteroresistant subpopulations remain within susceptible range of vancomycin MIC (1-2 $\mu\text{g/ml}$)

Table 2: CLSI and EUCAST breakpoints for vancomycin.

Second antibiotic administered as necessitated by lack of improvement and recurrent BSI within 60 days of vancomycin treatment should also be considered in case of hVISA infections. Prior

exposure to vancomycin is one of the considerable factors in clinical outcome analysis [21].

Role of Other Factors Contributing to Treatment Failure with hVISA/VISA Strains

The decreased action of vancomycin on hVISA/VISA may also be attributed to other mutation associated biological features like slower growth rate, reduced autolytic activity, thickened cell wall with reduced peptidoglycan cross-linking [22,23]. Various drug related factors also contribute to the poor outcomes. For example, lethal activity of vancomycin is compromised in the presence of structural communities like biofilms. Vancomycin is also less bactericidal than other antistaphylococcal penicillins and its activity falls between bacteriostatic tetracycline and bactericidal penicillins [24,25]. It is often reflected in the delayed clinical response evidenced by prolonged bacteraemia and persistent fever in MRSA endocarditis patients [26-28].

Thus the vancomycin treatment failure may be due to the enhanced virulence of organism or due to an intrinsic property of the drug or perhaps a combination of both. Further research is needed to find the relevance of hVISA in patients with vancomycin treatment failure. A standard screening test with high sensitivity and specificity for detecting hVISA/VISA needs to be implemented to better understand the prevalence and clinical impact of these organisms [29].

Role of Diagnostic Laboratory in Early Detection of hVISA/VISA

As heteroresistant subpopulations exist in strains with an MIC of 2 µg/ml, detection of hVISA phenotype and high vancomycin MIC values were directly related [30]. Detection of vancomycin heteroresistance needs careful selection of isolates that requires testing as it is not feasible to test all *S. aureus* isolates. The different methods employed for the detection of heteroresistance are described below.

Population study

As described by Hiramitsu *et al.* in 1997, specific inocula of MRSA are plated onto Brain Heart Infusion agar containing vancomycin at a concentration of 4 µg/ml. Any visible colony on the plates observed after incubation for 48 hours is considered heteroresistance [31].

Population analysis

Population analysis profile-area under the curve ratio (PAP-AUC): The colonies to be tested are incubated in Tryptone Soy broth for 24 hours. The colonies (undiluted and in dilutions of 1/10⁸ and 1/10⁵) are then spiral plated onto several BHI agar plates containing varying concentration of vancomycin from 0.5 to 8 µg/ml. A colony count is done on all plates after 48 hours of incubation at 35°C. The CFU/ml and vancomycin concentrations are graded and an area under the curve is obtained. A ratio is obtained by dividing the AUC of test strain with the AUC of the hVISA standard Mu3 strain that is plated along with the test strain. Values of 0.9 to 1.3 is considered hVISA [32].

Screen agars

A number of vancomycin screen agars have been proposed for the detection of hVISA. However the most popular one is the MHA5T agar which is Mueller Hinton agar incorporated with 5µg/ml of teicoplanin. A 2 McFarland test suspension is spot inoculated on the

plate and reading taken after 48 hours. Any growth is considered positive for hVISA [33].

Modified/Macrodilution E-test

A 2 McFarland standard suspension of the test strain is made. 200 µl of this suspension is pipetted onto a BHI plate and swabbed evenly. The vancomycin E-test strip is placed on the surface and the plate is incubated at 35°C for 48 hours. An MIC of 8 µg/ml or more is taken as heteroresistance [34].

Glycopeptide resistant detection (GRD) E-test

This method utilises the double sided E-strip containing serially increasing concentrations of vancomycin and teicoplanin on opposing sides and a nutritional supplement. The 0.5 McFarland standard suspension of the test strain is evenly inoculated onto Mueller Hinton agar supplemented with 5% blood and the E-strip is placed on the inoculum. Reading is taken after 24 and 48 hours of incubation. An MIC of 8 µg/ml or more with vancomycin or teicoplanin is taken as heteroresistance [35].

Detection of hVISA is challenging in clinical microbiology laboratories because reliable and practical method is not available for routine practice. However, MRSA with vancomycin MIC ≤ 2 µg/ml especially 1 µg/ml-2 µg/ml are more likely to result in vancomycin treatment failure due to hVISA/VISA infection. These isolates with vancomycin MIC of 1 µg/ml-2 µg/ml are suitable for screening the presence of hVISA phenotypes using macro E-test/GRD E-test. The MRSA isolates identified with either of criteria, Macro E-test (teicoplanin ≥ 12 µg/ml or teicoplanin ≥ 8 µg/ml and vancomycin ≥ 8 µg/ml) and GRD E-test (vancomycin/teicoplanin ≥ 8 µg/ml) is suggestive of the presence of hVISA phenotype. Further this hVISA isolates should be confirmed by PAP-AUC analysis (Gold standard). PAP-AUC ratio is interpreted as <0.9; VSSA, 0.9-1.3; hVISA, and >1.3; VISA (Figure 2).

Optimum detection of hVISA strains relies on testing of higher inoculum [10⁸ CFU for PAP/AUC analysis and 2 McFarland standard inoculum for macromethod E test], use of more nutritious media like BHIA, MHA supplemented with sheep/horse blood and longer incubation times (48 hrs) [36]. In spite of the availability of several screening assays such as modified E-test methods and screening agars, presence of hVISA strains can be confirmed by PAP/AUC analysis only [37]. Though PAP is labour intensive, costly and time consuming, it still remains the gold standard in assessing the heteroresistant populations.

Clinical markers combined with laboratory screening methods may assist clinicians in reassessing treatment options for hVISA infections. Correlation of *in vitro* results with efficacy studies in animal models or clinical outcomes is important for screening of the increasing levels of resistance. The duration of bacteremia, complications, and outcome should be correlated with the vancomycin MICs and hVISA status.

Molecular Characterisation of hVISA/VISA

The specific determinant for molecular characterisation of hVISA/VISA was not reported. As discussed earlier, mutation in TCRS and rpoB gene results in generation of hVISA/VISA strains. Combined analysis of clinical markers, laboratory diagnosis and screening for the presence of mutation in genes involved in cell metabolism helps to understand the clear mechanism of hVISA/VISA strains.

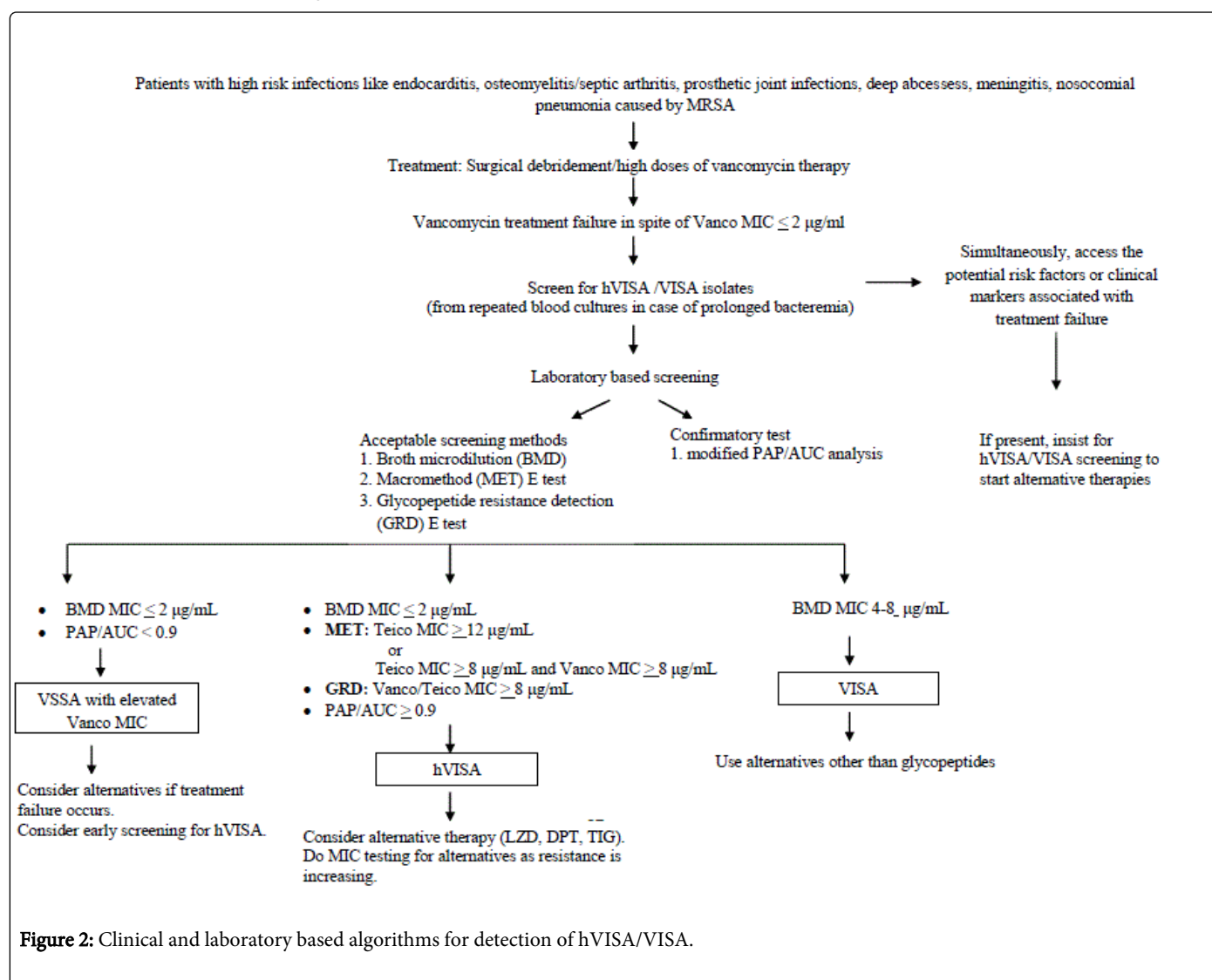
Alternative Therapies for hVISA/VISA Infections

Vancomycin is the drug of choice for invasive infections caused by multidrug-resistant *S. aureus* most notably nosocomially acquired methicillin-resistant *S. aureus* (MRSA). Clinical cure rate of vancomycin was found to be 35.5% in patients with MRSA associated nosocomial pneumonia [38]. All reported cases of hVISA and VISA was associated with high bacterial load infections and clinical success rate was found to be 31.8% for vancomycin and 60% in case of surgical debridement [39].

Reasons for the decline in efficacy of vancomycin in the treatment of invasive infections was found to be due to poor tissue and intracellular penetration of the drug, slow bactericidal effect, lack of interference with toxin production, loss of accessory gene-regulator function in MRSA [40,41]. Increasing reports of *in vitro* resistance and

treatment failures due to hVISA/VISA strains emphasize the need for newer therapeutic options. Administration of alternative therapies in case of treatment failure should be based on both clinical and laboratory findings. In addition to the treatment failure, other contributing factors includes adequate dose administration with less toxicity, trough levels monitoring remain as challenges in usage of vancomycin.

Fortunately, several other alternatives for treating hVISA/VISA infections include linezolid, quinupristin-dalfopristin, daptomycin, and tigecycline. All these are approved by the FDA. Though *in vitro* and animal studies data were available, clinical trials based efficacy rate was not released for the above mentioned newer antimicrobial agents.



Rifampin and fusidic acid

Combination therapy with rifampin and fusidic acid was found to possess good *in vitro* and in-vivo activity against multidrug resistant *S. aureus*. These drugs should always be used in combination with other anti-staphylococcal agent, as resistance develops rapidly with

monotherapy [42,43]. Oral rifampin and fusidic acid was reported to be successful against hVISA/VISA infections in patients with vancomycin treatment failure.

Linezolid

Linezolid, a completely synthetic oxazolidinone can be used for the therapy of *S. aureus* with reduced vancomycin susceptibility. Linezolid acts by inhibiting protein synthesis by binding with 50S ribosome. It is a bacteriostatic agent with good action against MRSA, hVISA and VISA infections, including high bacterial load infections like endocarditis, pneumonia, skin and soft tissue infections [44]. Linezolid is especially preferred for treating MRSA/hVISA/VISA pneumonia/lower respiratory tract infection (LRTI). It is also useful in treating patients not responding to vancomycin. Development of linezolid resistance against *S. aureus* is of great concern. A novel linezolid resistance (LRSA) mechanism carried on a mobile genetic element has been reported recently in cfr-constitutive LRSA outbreak in Madrid [45,46]. As high rate of toxicity has been found in linezolid administered patients, it is advisable to use it with caution in prolonged therapies.

Daptomycin

Daptomycin, a cyclic lipopeptide should be used with caution against high bacterial load *S. aureus* infection [47]. Daptomycin acts directly against cell membrane through Ca^{2+} dependent mechanism results in efflux of potassium and inhibition of protein, DNA and RNA synthesis. For high bacterial load infection the recommended dosage for daptomycin is 6mg/kg/day and for SSTIs are 4 mg/kg/day. *In vitro* animal studies have suggested that daptomycin possess slower rate of bactericidal activity against hVISA than VISA [48]. Cross-resistance between daptomycin resistance and hVISA/VISA are reported in a patient with endocarditis [49]. The highest rate of daptomycin non-susceptibility was reported in 15% of hVISA and 38% of VISA strains. High dose daptomycin (10 mg/kg/day) with trimethoprim-sulfamethoxazole has shown to be promising for treatment of hVISA/VISA infections [50].

Quinupristin-dalfopristin and tigecycline

Quinupristin-dalfopristin (QD), a combination of two streptogramins has potent *in vitro* activity against a range of hVISA, VISA and MRSA strains. It acts by inducing conformational changes in the ribosome. The recommended dosage is 7.5 mg/kg q 8 h-12 h for skin and soft tissue infection, bone and joint infections. The MIC 90 for hVISA and VISA strains was found to be 1 µg/ml [51].

Tigecycline belongs to tetracycline family and was the first glycylcycline used in clinical cases. Tigecycline binds with 30S subunit of ribosome and inhibit protein synthesis. It is active against MSSA and MRSA strains and small numbers of VISA strains with MIC90 of 0.12 µg/ml to 1 µg/ml [52,53].

Newer antimicrobials against hVISA/VISA infections in development

Dalbavancin, a semisynthetic lipoglycopeptide has good *in vitro* activity against *S. aureus* with MIC 0.015 µg/ml to 0.5 µg/ml by inhibiting cell wall synthesis. It is effective in patients infected with *S. aureus* that are resistant to vancomycin, linezolid and quinupristin-dalfopristin [54]. MICs was found to be higher for hVISA/VISA strains (0.06 µg/ml to 2 µg/ml) and thus higher concentrations was required to achieve in vivo killing. Its efficacy against VISA strains have also been demonstrated in animal models [55]. Dalbavancin is

given as 1000 mg intravenously on day1 and followed by 500mg on day 8 sustains the plasma concentration to 20 µg/ml [56].

Oritavancin, a lipoglycopeptide possess notable *in vitro* activity against VRSA strains and reduced bactericidal activity against VISA strains by disrupting the cell membrane [57,58]. Telavancin, a semisynthetic lipoglycopeptide and derivative of vancomycin has MIC ranging between 0.03 and 1 µg/ml against methicillin resistant *S. aureus* strains, and 0.125 to 1 µg/ml for VISA strains [59-61].

Newer cephalosporins like ceftaroline and ceftobiprole possess good *in vitro* activity against hVISA and VISA strains with MIC range of 0.25 µg/ml to 4 µg/ml and <2 µg/ml respectively [62]. Through animal studies, ceftaroline was found to be superior to vancomycin, linezolid, teicoplanin, and arbekacin in treatment of MRSA infections [63]. In 2005, *Jacqueline et al.* reported that ceftaroline has high bactericidal activity against hVISA compared with linezolid/vancomycin treatment [64]. Similarly, ceftobiprole is also reported to have high bactericidal activity against hVISA strains than vancomycin [65].

Though various studies have reported the successful therapies against hVISA/VISA infections with alternative antimicrobials, potential concerns including toxicity with prolonged linezolid use, cross-resistance with lipoglycopeptides, and low-level daptomycin non-susceptibility should be taken into consideration. To overcome these shortcomings, vancomycin is combined with other alternatives in treatment of severe MRSA infections. Reasons behind the combination therapy includes broadening the spectrum of anti-staphylococcal activity to include VISA/hVISA strains, preventing the emergence of *S. aureus* with reduced vancomycin susceptibility, enhancing bactericidal activity, inhibiting toxin production and facilitating the penetration into cells and tissues not reached by vancomycin.

Successfully Treated hVISA/VISA Cases: Combination Therapy

The combination of vancomycin or daptomycin and a β-lactam antibiotic were also studied for treating hVISA/VISA infection. The synergistic activity of β-lactam including ceftaroline, cefazolin, and piperacillin-tazobactam has been evaluated with vancomycin or daptomycin for therapy [66-68]. Addition of β-lactam antibiotic to either vancomycin or daptomycin enhances the activity of vancomycin/daptomycin by interacting with cell wall synthesis. However, further studies are warranted to elucidate the interaction in improved killing of MRSA.

In patient with MRSA bacteremia and are failing with vancomycin therapy were successfully treated with linezolid in combination with rifampin plus fusidic acid or linezolid alone or with trimethoprim-sulfamethoxazole (orally 160 mg and 800 mg daily). Studies have reported those hVISA/VISA endocarditis were recovered from infection with an alternative therapy of linezolid alone or in combination with rifampin or fusidic acid [69,70].

For patient with acute MRSA cholecystitis, initially treated with vancomycin for 10 weeks results in poor outcome and hVISA development with an MIC of 8 µg/ml was documented. This patient was successfully treated with the combination of linezolid (600 mg twice a day) plus trimethoprim-sulfamethoxazole (160 mg and 800 mg) plus doxycycline (100 mg orally) twice a day [71]. Similarly in patient with septic arthritis, developed hVISA and treatment failure was completely recovered while treated with linezolid alone or

linezolid plus rifampin and fusidic acid [70]. Patient with endocarditis who failed with both vancomycin and daptomycin therapy were successfully treated with linezolid (600 mg q 12 hrs) and fusidic acid (500mg q 8hrs) or linezolid with trimethoprim-sulfamethoxazole plus quinupristin-dalfopristin [71].

Conclusion

Presence of hVISA/VISA strains in serious MRSA infections may lead to treatment failure. As the therapeutic options were limited, appropriate use of vancomycin prevents the development of vancomycin resistance. Optimal detection methods are essential for proper guidance of therapeutic decision making and complete understanding the impact of hVISA infection. The clinician can continue to use vancomycin as recommended by Infectious Diseases Society of America guidelines. Except, for patients who are not responding to vancomycin and present with risk factors of hVISA/VISA infections, alternative therapies can be considered. Treating with daptomycin should be used with caution for hVISA/VISA infection, because of the potential for cross resistance.

Early detection/surveillance of hVISA/VISA strains and standard infection control practices for the prevention of spread of resistance strains should be strictly followed in all hospital settings. Detection of mutation involving with TCRS and rpoB gene for development of heteroresistance may facilitate earlier identification of hVISA/VISA strains and thus its associated treatment failure. Even though alternatives were available against hVISA/VISA infections, treatment guidelines have to be redefined with caution as only limited information are available.

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