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REVIEW

Emerging Antimicrobial Strategies Against Heterogeneous and Vancomycin-Intermediate *Staphylococcus aureus*

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Abstract: Heterogeneous vancomycin-intermediate and vancomycin-intermediate *Staphylococcus aureus* (hVISA and VISA) presents significant therapeutic challenges due to high treatment failure rates and limited options. Conventional monotherapies, including daptomycin and linezolid, are often compromised by cross-resistance and inconsistent efficacy. Combination therapies incorporating β-lactams, quinolones, or lipopeptides with vancomycin exploit synergistic mechanisms (eg, the "seesaw effect") but exhibit variable success depending on bacterial strain, drug concentration, and experimental models. Novel antimicrobials, such as next-generation glycopeptides (LY333328, oritavancin, YV4465), synthetic agents (pyridyl disulfides, alpha-amyrin), and natural derivatives (plant flavonoids, cyanobacterial metabolites), have demonstrated enhanced activity against VISA/hVISA by disrupting membranes, suppressing virulence, or reversing resistance. Antimicrobial peptides and non-classical agents (eg, nybomycin, telomycin) further expand therapeutic options by targeting RNA degradation, biofilms, or toxin production. Additionally, advanced drug delivery systems, including nanoemulsions and nanoliposomes, improve drug stability, biofilm penetration, and localized efficacy. Despite these promising advances, clinical translation remains challenging, requiring rigorous validation of synergistic mechanisms, optimized dosing strategies, and resistance mitigation approaches. Continued innovation in antimicrobial development is essential to address the growing threat of multidrug-resistant *Staphylococcus aureus* infections.

Keywords: hVISA, VISA, monotherapy, combination therapy, novel antimicrobials, drug delivery system

Introduction

Staphylococcus aureus, a ubiquitous pathogen colonizing human skin, nasal passages, and mucosal surfaces, is implicated in infections ranging from mild cutaneous conditions to life-threatening systemic diseases.[1,2] Its public health significance stems from its versatile pathogenicity and escalating antibiotic resistance, exacerbated by the widespread misuse of antimicrobials, particularly in nosocomial settings. Since the emergence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the UK in 1961, it has evolved into a global health crisis, contributing to over 100,000 deaths in 2019 alone.[3] Vancomycin has long been the "last line of defense" in the treatment of MRSA infections.[4] However, the emergence of heterogeneous and vancomycin-Intermediate *Staphylococcus aureus* (hVISA and VISA) strains in recent decades has significantly compromised vancomycin's clinical utility.[5,6]

VISA strains exhibit reduced susceptibility to vancomycin without meeting the threshold for full resistance, while hVISA populations consist predominantly of vancomycin-susceptible *Staphylococcus aureus* with a subpopulation displaying intermediate resistance.[7] The presence of vancomycin heterogeneity and intermediate resistance strains suggests that these infections may require higher doses of the drug or extended treatment durations for effective therapy.[6]

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The resistance mechanisms of VISA are predominantly linked to structural and functional alterations in the bacterial cell wall.[8,9] Vancomycin exerts its bactericidal activity by binding to cell wall precursor molecules (D-Ala-D-Ala termini of lipid II), thereby inhibiting peptidoglycan biosynthesis. VISA strains exhibit a characteristically thickened cell wall, a phenotype attributed to dysregulation of the peptidoglycan biosynthesis pathway and elevated cross-linking density between peptidoglycan polymers. This thickened cell wall architecture serves as a primary resistance mechanism by impeding vancomycin diffusion to its intracellular targets. Genomic analyses further reveal that VISA resistance correlates with mutations in key regulatory loci, eg, *walKR, rpoB, vraSR, graRS* and *mprF*. These genetic modifications are hypothesized to alter membrane charge and permeability, reducing drug influx while enhancing efflux pump activity.[8,9]

The global emergence of antibiotic-resistant pathogens, particularly VISA and vancomycin-resistant *Staphylococcus aureus* (VRSA), has intensified the demand for novel antimicrobial therapies. Conventional antibiotics, such as daptomycin, are becoming increasingly ineffective due to escalating resistance, necessitating innovative therapeutic approaches. At the same time, the diagnostic difficulty of hVISA—where routine MIC testing in labs fails to detect it and hospital labs do not perform population analysis—exacerbates the challenges in treating patients with hVISA. Current clinical management of hVISA and VISA infections often relies on vancomycin dose escalation or combination therapy with β-lactams or daptomycin.[6] However, these strategies demonstrate limited efficacy and carry risks of nephrotoxicity and other adverse effects. Consequently, research efforts are increasingly focused on developing targeted antimicrobial agents and alternative treatment modalities. Promising avenues include new antibiotics, antimicrobial peptides, synthetic agents, natural derivatives as well as drug delivery system. Such advancements not only address the urgent clinical need for VISA management but also contribute to mitigating the broader antimicrobial resistance crisis.

Monotherapy

The clinical management of hVISA and VISA infections is challenged by high rates of vancomycin treatment failure, compounded by limited therapeutic alternatives.[9] Current options include daptomycin, linezolid, ceftaroline, trimethoprim/sulfamethoxazole, tigecycline, and quinupristin/dalfopristin, though only daptomycin and linezolid have been studied extensively.[6]

Daptomycin, an FDA-approved lipopeptide for *Staphylococcus aureus* bloodstream infections and right-sided endocarditis including methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA,[10,11] shows reduced utility against hVISA/VISA strains. Notably, its use has been associated with the increase in the minimum inhibitory concentration (MIC) of vancomycin and emerging daptomycin nonsusceptibility in vitro.[6] Genomic studies reveal that mutations in yycH (a cell wall stress response regulator), mprF (phosphatidylglycerol lysyltransferase), and dltA (D-alanylation pathway) confer cross-resistance to daptomycin in hVISA/VISA strains, complicating its clinical efficacy.[12,13]

Linezolid, an oxazolidinone inhibiting ribosomal protein synthesis, remains controversial for hVISA/VISA management. While observational studies report clinical success with linezolid monotherapy or combination regimens,[14,15] in vitro susceptibility testing often fails to correlate with these outcomes.[16] We hypothesize that this may be related to some factors, eg immune modulation, and intracellular activity. This discrepancy underscores the need for robust clinical trials to clarify linezolid's role and optimize dosing strategies. Furthermore, prolonged linezolid use carries risks of myelosuppression and mitochondrial toxicity, necessitating careful risk-benefit evaluation.

Collectively, these limitations highlight the urgent need for standardized susceptibility testing, pharmacokinetic/pharmacodynamic optimization, and novel therapeutics targeting hVISA/VISA-specific resistance mechanisms.

Combination Therapy

The therapeutic potential of antibiotic combinations against hVISA/VISA infections lies in their ability to generate synergistic antibacterial effects, offering enhanced clinical efficacy compared to monotherapy (Table 1). This approach has emerged as a viable strategy for managing these challenging infections, with investigated combinations spanning glycopeptides, β-lactams, quinolones, oxazolidinones, lipopeptides, phosphonic acid derivatives, and phenothiazines. Vancomycin exhibits synergistic antibacterial activity when combined with β-lactam antibiotics, quinolones, aminoglycosides, rifamycins, sulfonamides, and oxazolidinones.

Table 1 Combination Therapy for Vancomycin-Nonsusceptible *Staphylococcus Aureus*

Number	Combination Drug Therapy	Model	Pathogen	Effect	Publication Date
1	Trovafloxacin,ampicillin-sulbactam	In vitro	VISA	a) Trovafloxacin has limited effect on VISA. b) Ampicillin-sulbactam can rapidly kill bacteria, but regrowth may occur. c) Neither agent alone was sufficient to combat VISA. d) In combination, they may exert synergistic effects against certain VISA.	2000[17]
2	Vancomycin, oxacillin, ampicillin, cefoxitin, cefmetazole, penicillin G, piperacillin and imipenem	In vitro	hVRSA	a) Within a certain concentration range, the ampicillin, oxacillin, imipenem and cefmetazole, when combined with vancomycin, exhibited synergistic effects.b) Within a certain concentration range, all seven antibiotics showed antagonistic interactions.	2001[18]
3	Vancomycin, teicoplanin, cloxacillin and cefotaxime	In vitro and vivo	MSSA, MRSA, hGISA and GISA	a) In vitro, the combination of glycopeptides and β-lactam antibiotics exhibited synergistic effects against MSSA, MRSA, h-GISA and GISA. b) In vivo, this combination did not show significant synergistic effects.	2005[19]
4	Linezolid, imipenem and vancomycin	In vitro and vivo	hGISA and GISA	a) In vitro, the combination of linezolid and imipenem exhibited synergistic effects. b) In vitro, linezolid reduced the antibacterial activity of vancomycin. c) In vivo, linezolid monotherapy or combination therapy showed similar bactericidal effects, having a discrepancy with vitro experiments.	2010[14]
5	Ceftobiprole and vancomycin	In vitro and vivo	VISA and MRSA	a) Ceftobiprole monotherapy was effective against experimental endocarditis caused by VISA. b) Subtherapeutic doses of ceftobiprole in combination with vancomycin exhibited synergistic effects.	2011[20]
6	Daptomycin, nafcillin	In vitro and vivo	VISA	a) The combination of daptomycin and nafcillin exhibits synergistic antibacterial effects against 55% of VISA. b) The synergistic antibacterial activity was stronger when daptomycin was used at a dosage of 10 mg/kg in combination with nafcillin.	2012[21]
7	Vancomycin, ceftaroline and oxacillin	In vitro	VISA and hVISA	a) The combination of vancomycin with ceftazidime or ofloxacin exhibited synergistic effects against certain VISA and hVISA. b) β-lactam antibiotics enhanced the interaction between vancomycin and the bacterial cell wall.	2013[22]
8	Linezolid, vancomycin, rifampicin	In vitro and vivo	MRSA and GISA	a) The combination of linezolid and rifampicin significantly inhibited bacterial growth and improved the inflammatory response. b) Linezolid (at 1 MIC) combined with rifampicin (at 1/4 MIC) or vancomycin (at 1/2 MIC) exhibited synergistic antibacterial activity against GISA.	2014[23]
9	Vancomycin and piperacillin-tazobactam	In vitro	MRSA and VISA	The combination of vancomycin and piperacillin-tazobactam enhanced the antibacterial activity against MRSA and VISA, but bacterial regrowth may still occur.	2014[24]
10	Fosfomycin, imipenem, ceftriaxone and amoxicillin-clavulanic acid	In vitro and vivo	GISA	a) The combination of fosfomycin/imipenem and fosfomycin/ceftriaxone demonstrated significantly superior efficacy in treating infective endocarditis caused by MRSA or GISA compared to vancomycin. b) The combination of fosfomycin and imipenem exhibited higher activity.	2015[25]
11	Vancomycin, clindamycin, ciprofloxacin, gentamicin, rifampicin and trimethoprim/sulfamethoxazole	In vitro	VISA, hVISA and VSSA	a) The combination of vancomycin and ciprofloxacin, gentamicin or trimethoprim/sulfamethoxazole exhibited synergistic effects against certain VISA, h-VISA and VSSA. b) The combination of rifampicin and quinolones can slow down the development of resistance. c) The combination of clindamycin and trimethoprim/sulfamethoxazole was not effective against VISA and hVISA.	2016[26]
12	Vancomycin, teicoplanin, cefazolin, cefmetazole, cefotaxime and cefepime	In vitro	hVISA and VISA	The antibacterial activity of vancomycin/teicoplanin against hVISA and VISA was enhanced when combined with extremely low concentrations of cephalosporins.	2017[27]
13	Vhioridazine and dicloxacillin	In vitro	VISA and MRSE	a) The combination of thioridazine and dicloxacillin exhibited synergistic effects against 3/4 VISA. b) The combination of thioridazine and dicloxacillin did not exhibit synergistic effects against MRSE.	2017[28]
14	Tedizolid, vancomycin, teicoplanin, fusidic acid, rifampicin	In vitro and vivo	GISA, hGISA, GRSA and MRSA	a) Tedizolid exhibited good in vitro activity against MRSA, hGISA, and GISA. b) No significant synergy was observed between glycopeptide antibiotics and rifampin or fusidic acid in vitro. c) The combination of teicoplanin and rifampin showed the best antibacterial effect both in vitro and vivo.	2018[29]
15	Cefazolin, vancomycin and daptomycin	In vitro	MRSA and VISA	The addition of cefazolin slowed down the development of resistance in MRSA.	2018[30]

(*Continued*)

Table 1 (Continued).

Number	Combination Drug Therapy	Model	Pathogen	Effect	Publication Date
16	Vancomycin, cefazolin, cefepime, ceftaroline and nafcillin	In vitro	VSSA, hVISA and VISA	a) The combination of vancomycin with four β-lactam antibiotics significantly reduced its minimum inhibitory concentration. b) The combination of vancomycin with four β-lactam antibiotics exhibited synergistic antibacterial activity against VSSA, hVISA, and VISA.	2018[31]
17	Oxacillin and vancomycin	In vitro	hVISA, MRSA and MSSA	a) The combination of oxazolidinone and vancomycin exhibited synergistic effects against hVISA and MRSA. b) The addition of oxazolidinone reduced the minimum inhibitory concentration of vancomycin and enhanced antibacterial activity of vancomycin.	2019[32]
18	Vefazolin, cefmetazole, cefotaxime, cefepime, sulbactam and daptomycin	In vitro	VISA and hVISA	a) The combination of daptomycin and sulbactam did not exhibit bactericidal or bacteriostatic effects. b) Cephalosporins can enhance the antibacterial activity of daptomycin. c) Sulbactam can further enhance the activity of the daptomycin/cephalosporin combination against certain strains.	2019[33]
19	Vancomycin, cefotaxime, imipenem and meropenem	In vitro	VISA, hVISA and VSSA	a) The combinations of vancomycin with imipenem, meropenem or cefixime exhibited varying degrees of synergistic effects against VISA, hVISA and VSSA. b) With the combination of imipenem showed the most pronounced synergistic activity.	2021[34]
20	Fosfomycin, vancomycin, daptomycin, linezolid, ceftaroline and cefazolin	In vitro	VISA, VRSA, DRSA and LRSA	a) The combinations of fosfomycin/ceftaroline and fosfomycin/cefazolin exhibited synergistic effects. b) The combination of fosfomycin/linezolid showed synergistic effects in most strains. c) The combination of fosfomycin/vancomycin exhibited synergistic effects in only a few strains.	2022[35]
21	Viprofloxacin, levofloxacin and rifampin	In vitro	VSSA, VISA and hVISA	a) Ciprofloxacin and levofloxacin exhibited synergistic effects with rifampin, with ciprofloxacin showing better results. b) High MIC values of fluoroquinolones can predict their synergistic effects.	2023[36]

Abbreviations: DRSA, daptomycin-resistant *Staphylococcus aureus*; GISA, glycopeptide-intermediate *Staphylococcus aureus*; GRSA, glycopeptide-resistance *Staphylococcus aureus*; hGISA, hetero-glycopeptide-intermediate *Staphylococcus aureus*; hVISA, hetero-vancomycin-intermediate *Staphylococcus aureus*; hVRSA, hetero-vancomycin-resistant *Staphylococcus aureus*; LRSA, linezolid-resistant *Staphylococcus aureus*; MRSA, meticillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; VSSA, vancomycin-susceptible *Staphylococcus aureus*.

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β-Lactam Combinations

Vancomycin demonstrated synergistic activity when combined with β-lactams including nafcillin,[31] oxacillin,[32] cloxacillin,[19] piperacillin-tazobactam,[24] cefazolin, cefoxitin, ceftazidime,[30,31] cefmetazole, cefotaxime, cefepime,[19,27] ceftobiprole,[20] cefixime, imipenem, and meropenem.[34] This synergy stems from β-lactam-mediated inhibition of penicillin-binding proteins (PBPs), which alters peptidoglycan cross-linking and modifies cell wall architecture.[34] This alteration in the bacterial cell surface structure facilitates the binding of VAN to its specific target sites.[37] These structural changes facilitate vancomycin binding to its molecular targets through the "seesaw effect" - a phenomenon where β-lactam-induced cell wall stress increases bacterial susceptibility to glycopeptides by modulating PBP expression and peptidoglycan biosynthesis.[22,38] Notably, Aritaka et al[24] reported that only ampicillin, oxacillin, imipenem, and cefmetazole showed synergy with vancomycin, while cephalothin, penicillin G, and piperacillin did not, contradicting other studies.[27,32,34] This discrepancy may reflect concentration-dependent effects, as sub-MIC β-lactam levels can paradoxically induce antagonism.[18,39] We hypothesize that other factors, such as differences in testing media, strain genetics, or endpoints, could also explain this phenomenon.

Non-β-Lactam Synergy

Vancomycin combinations with ciprofloxacin, gentamicin, and trimethoprim/sulfamethoxazole exhibited anti-VISA /hVISA synergy,[26] though conflicting data exist for gentamicin.[40] Teicoplanin demonstrated enhanced efficacy when paired with cefazolin, cefmetazole, cefotaxime, cefepime,[27] or rifampicin.[29] However, oxazolidinones like tedizolid showed superior anti-GISA activity compared to glycopeptides.[29] Promising alternatives include: ampicillin-sulbactam with trovafloxacin[17] or arbekacin;[41] ciprofloxacin-rifampicin combinations;[36] linezolid paired with imipenem[14] or rifampicin;[23] fosfomycin combined with imipenem, ceftriaxone, or linezolid;[25,35] daptomycin synergized with nafcillin[21] or cephalosporins,[33] enhanced by sulbactam in triple therapy;[33] thioridazine-dicloxacillin targeting VraSR-mediated cell wall metabolism.[28]

Experimental-Clinical Disconnects

While existing studies demonstrate promising evidence for combination therapies targeting hVISA and VISA, substantial inconsistencies and methodological limitations persist across these investigations. These discrepancies likely stem from heterogeneous experimental designs, divergent methodologies, and strain-specific variations, underscoring the necessity for standardized approaches to develop reliable therapeutic paradigms.

First, discrepancies in antimicrobial synergy emerge across different susceptibility testing modalities. Alejandro et al[19] reported in vitro synergy between glycopeptides (vancomycin/teicoplanin) and β-lactams (cloxacillin/cefotaxime) against VISA strains, yet failed to replicate this synergy in murine infection models - a critical limitation for clinical translation. Subsequent susceptibility testing revealed synergistic interactions between vancomycin-cefotaxime/imipenem/meropenem combinations against vancomycin-susceptible *Staphylococcus aureus* (VSSA), VISA, and hVISA strains. However, time-kill assays demonstrated vancomycin-meropenem synergy exclusively in VISA strains, with no significant interaction observed against VSSA.[34] This dichotomy between in vitro susceptibility data and in vivo efficacy suggests complex pharmacokinetic-pharmacodynamic interactions and host-pathogen dynamics that current experimental models may inadequately replicate.

Second, antimicrobial concentration profoundly influences combination therapy outcomes. In a VISA endocarditis rat model, very-low-dose ceftobiprole (0.25 mg/kg) combined with standard vancomycin dosing achieved superior bacterial clearance compared to low-dose ceftobiprole (5 mg/kg) combinations.[20] This dose–response relationship was corroborated in vitro, where 0.5 μg/mL imipenem enhanced vancomycin efficacy more significantly than 0.125 μg/mL concentrations.[36] Similarly, quinolone-rifampicin combinations exhibited concentration-dependent synergy, with higher quinolone concentrations improving bactericidal activity.[36] These findings emphasize the critical need for optimized dosing regimens that consider MIC variations among vancomycin-nonsusceptible strains.

Third, substantial inter-strain variability in therapeutic responses necessitates precision medicine approaches. Clinical isolates demonstrate heterogeneous susceptibility profiles to both monotherapy and combination regimens, mandating strain-specific antimicrobial selection and dose adjustment.[20] This phenotypic diversity likely originates from differential expression of resistance mechanisms across genetic lineages.

The mechanistic basis for antimicrobial synergy remains incompletely characterized. Following Hiramatsu's seminal 1997 reported on hVISA emergence in Japanese hospitals,[42] subsequent research has implicated multiple-resistance pathways: 1) altered cell wall architecture (thickening/structural remodeling), 2) modified membrane surface charge distribution, 3) differential penicillin-binding protein expression/activity, and 4) genetic mutations affecting membrane phospholipid biosynthesis.[33,43–45] Notably, vancomycin exposure in resistant strains induces cell wall precursor accumulation through impaired autolytic activity, creating a paradoxical bacteriostatic effect that may potentiate β-lactam efficacy.

Despite current limitations, combination therapies retain significant clinical potential for vancomycin-nonsusceptible *Staphylococcus aureus* infections. Future research priorities should include: 1) development of pharmacokinetic models to optimize dosing regimens; 2) large-scale clinical trials validating experimental findings. Such efforts will facilitate the creation of targeted, evidence-based treatment algorithms for these challenging infections.

Novel Antimicrobial Agents

Given the limitations of traditional antibiotics, novel antimicrobial agents offer a promising frontier for combating hVISA and VISA. These encompass new antibiotics, antimicrobial peptides (AMPs), synthetic agents, natural derivatives, and other (Table 2).

New Antibiotics

Studies reveal that optimized glycopeptides (eg, LY333328, oritavancin, YV4465)[40,51–53] achieve dose-dependent bactericidal effects in vitro by improving pharmacokinetic parameters (eg, AUC/MIC ratios) and enhancing target binding. Oritavancin retains bacteriostatic activity (2–3 log reduction) against certain VISA strains even at high inoculum densities (10^7 CFU/mL), while YV4465 reduces bacterial load by ~2 $\log_{10}$ CFU/g in murine infection models. Fluoroquinolones (levonadifloxacin and BMS-284756),[48,49] oxazolidinones (tedizolid and AZD2563),[56,57] and fluoroketolides (CEM-101)[47] exhibit enhanced potency against multidrug-resistant strains (including hVISA, DNS, and linezolid-resistant isolates), with MIC_{90} values 2–16 times lower than conventional agents, and remain effective against strains carrying the cfr resistance gene. Dalbavancin shows bactericidal curves comparable to MSSA against hVISA and DNS isolates, suggesting its capacity to penetrate biofilms and suppress resistance mutations.[55] Notably, while apramycin shows no existing resistance mechanisms, its attenuated activity under high inoculum conditions highlights the need to optimize dosing strategies or combination therapies.[46] The novel carbapenem ME1036[50] demonstrated superior in vivo efficacy (>3 log reduction) against VISA in immunocompromised murine models, while the β-lactam RWJ-54428[54] exhibited potent broad-spectrum activity (MIC_{90} ≤2 mg/L) against glycopeptide-intermediate *Staphylococcus aureus*, aligning with its MRSA-targeting profile. Collectively, these antibiotics address VISA/hVISA infections through enhanced target specificity, prolonged half-lives, and evasion of resistance pathways, offering transformative options for complex infections such as endocarditis. However, they are currently in preclinical studies.

Antimicrobial Peptides (AMPs)

The semisynthetic lantibiotic NVB333 exhibits potent in vivo activity in murine thigh and bronchoalveolar infection models against MRSA and VISA, achieving >3-log CFU reductions despite modest MICs, with efficacy driven by high plasma exposure (AUC/MIC = 138) and lung penetration.[58] NAI-107, another lantibiotic, shows dose-proportional bactericidal effects in immunocompromised models, reducing MRSA and GISA loads by 3-log in rat endocarditis and granuloma pouch infections, sustained by trough plasma levels exceeding its MBC.[59] The cationic peptide omiganan inhibits VISA, hVISA, and VRSA at MIC_{90} ≤32 μg/mL, unaffected by vancomycin resistance mechanisms,[61] while melittin (Mel)-loaded non-ionic surfactant vesicles (NISVs) disrupt membrane integrity in VISA, MRSA, and clinical isolates, enhancing dermal penetration and bacterial clearance in porcine skin models.[60] Engineered lantibiotics like nisin

Table 2 Details About the Novel Antimicrobial Agents

Classification	Name	MIC (μg/mL)	MIC $_{90}$ (μg/mL)	MIC $_{50}$ (μg/mL)	Pathogen	Characteristic	Publication Date
Novel Antibiotics							
	Apramycin	_	16	8	VISA	Apramycin appears highly selective for bacterial ribosomes	2018[46]
	CEM-101	_	>16	>16	hVISA/ VISA	Addressing therapy of MLSB-resistant (R) species	2009[47]
	BMS-284756	0.5	_	_	hVISA	A novel quinolone that lacks a fluorine at the C-6 position and possesses a difluoromethoxy group at the C-8 position	2002[48]
	Levonadifloxacin		0.5	0.25	hVISA	A broad-spectrum benzoquinolizine fluoroquinolone	2020[49]
	ME1036	_	_	_	VISA	A novel parenteral carbapenem	2008[50]
	LY333328	_	_	_	GISA	A glycopeptide antibiotic	2000[40]
	Oritavancin	_	_	_	VISA	A semisynthetic lipoglycopeptide, that inhibits the biosynthesis of bacterial cell wall peptidoglycan by binding to either d-Ala-d-Ala- or d-Ala-d-Laccontaining residues in peptidoglycan precursors	2011[51,52]
	YV4465	0.44	_		VISA	A new glycopeptide antibiotic	2015[53]
	RWJ-54428	_	1	0.12	GISA	A new parenteral cephalosporin	2002[54]
	Dalbavancin	_	0.125	0.06	hVISA/ VISA	A new second-generation semisynthetic lipoglycopeptide	2020[55]
	AZD2563	_	2	1	hVISA	A novel oxazolidinone, inhibits protein synthesis by binding to domain V of the 23S rRNA and thereby blocking formation of the initiation complex	2003[56]
		_	1	1	VISA		
	Tedizolid	_	0.5	_	hVISA/ VISA	A next-generation oxazolidinone	2015[57]
Antimicrobial Peptides							
	NVB333	_	16	8	VISA	A novel semisynthetic lantibiotic, binding to the pyrophosphate-sugar moiety	2016[58]
	NAI-107	0.5	_	_	GISA	A lantibiotic active against multidrug-resistant Gram-positive pathogens	2011[59]
	Melittin	6.25~25	_	_	VISA	A principal component of honeybee venom and cationic α-helical peptide consisting of 26 amino acids with amphipathic characteristics	2021[60]
	Omiganan	_	32	16	hVISA/ VISA	A novel topical cationic peptide	2008[61]
	Nisin V	_	1.25	0.375	hVISA	A member of the lantibiotic family of antimicrobial peptides	2010[62]
Synthetic Agents							
	Allicin-inspired pyridyl disulfides	50	_	_	hVISA/ VISA	A electrophilic reagent in the synthesis of asymmetric (mixed) disulfides that mimic the chemical reactivity of allicin	2017[63]
	Alpha-amyrin	_	_	_	VISA	An anti-biofilm agent	2023[64]
	Aryl-4-guanidinomethylbenzoate	0.5~>256	_	_	VISA	One of the design, synthesis, and biological evaluation of novel guanidine derivatives	2008[65]
	N-aryl-4-guanidinomethylbenzamide	2~>256					
	Benzo-heptacontaining cycloalkane derivative	_	_	_	VISA	A new type diapophytoene desaturase inhibitor	2018[66]

(*Continued*)

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Table 2 (Continued).

Classification	Name	MIC (μg/mL)	MIC $_{90}$ (μg/mL)	MIC $_{50}$ (μg/mL)	Pathogen	Characteristic	Publication Date
Natural Derivatives	8-Hydroxy-cycloberberine derivatives	0.25~>64			hVISA/ VISA	One of a series of new 1 derivatives	2019[67]
	Vancomycin derivatives	_	0.06~64	_	VISA	A series of new vancomycin analogues carrying various sugar moieties on the seventh-amino acid phenyl ring and lipophilic substitutions on vancosamine	2018[68]
	9,10-dihydroacridine derivatives	2~4 (B1); 0.5 (B2)	_	_	VISA	A new and effective molecular scaffold	2021[69]
	Retapamulin	_	0.12	0.06	VISA	A novel, semisynthetic antimicrobial agent	2013[70]
	Benzothiazole compound 7a	<0.03125~0.0625	_	_	VISA	A new series of dual low nanomolar benzothiazole inhibitors of bacterial DNA gyrase and topoisomerase IV	2023[71]
	Chroman and coumaran derivatives	_	_	_	VISA	The novel inhibitors of staphyloxanthin virulence factor	2017[72]
	Diapophytoene desaturase	_	_	_	VISA	A potential novel target for intervening in the biosynthesis of the virulence factor staphyloxanthin	2018[73]
	Bis-indolic derivatives	1~>128	_	_	VISA	The bis-indolic compounds	2015[74]
	Aminoalkylamides of eremomycin	_	_	_	GISA	The new eremomycin amides	2020[75]
	1-(1H-indol-3-yl) ethanamine derivatives	8~>128	_	_	VISA	The substituted indolic derivatives	2011[76]
	Myricetin	16	_	_	VISA	A flavonoid capable of inhibiting several *S. aureus* virulence factors without influencing on bacterial growth	2020[77]
	Thieno[2,3-d] pyrimidinedione derivatives	2~>32	_	_	VISA	The heterocyclic compounds	2012[78]
	Achyrofuran	0.07	_	_	VISA	A prenylated dibenzofuran	2013[79]
	Blue green microalgae	32~64			VISA	One of the groups of organism from which biochemically active natural products have been isolated.	2006[80]
	Galangin	32	_	_	VISA	A naturally occurring flavonol	2017[81]
	Valencia orange oil	_	_	_	VISA	A plant derived essential oil	2012[82]
	Soybean glycinin basic subunit	_	_	_	VISA	A globulin storage protein of soybean consisting of an acidic and basic polypeptide chain linked by a single disulfide bond	2016[83]
	Pterostilbene	_	_	_	VISA	A methoxylated resveratrol derivative	2017[84]
	Anisochilus carnosus acetone extract	0.33 ± 0.14	_	_	VISA	Three extracts from 10 commonly used south Indian herbs for antibacterial activity	2020[85]
	Quercetin–pivaloxymethyl conjugate	16	_	_	VISA	A prodrug of quercetin	2018[86]
		32	_	_	hVISA		
	Pseudomonas aeruginosa extracts	_	_	_	VISA	The production of small molecular substances	2017[87]
	Pterostilbene	_	_	_	VISA	A methoxylated resveratrol derivative	2017[84]

Other Agents	Sodium new houttuyfonate	64	_	_	VISA	Sodium new houttuyfonate is a chemically stable derivative of houttuynin; Berberine is an isoquinoline alkaloid obtained from plants	2020[88]
	Berberine chloride	512	_	_			
	1/2 of sodium new houttuyfonate and berberine chloride	32	_	_			
	Telomycin	_	_	_	VISA	An antibacterial metabolite extracted from phageresistant S. abietis strain	2024[89]
	Nybomycin	0.25	_	_	VISA	A curing bacteria of antibiotic resistance and reverse antibiotic	2012[90]
	Gemcitabine and its derivative CP-4126	0.06 ~ 4.22	_	_	GISA	A cytotoxic nucleoside analogue	2012[91]
	Iclaprim	0.25	_	_	VISA	A folic acid synthesis inhibitor	2019[92]
	RnpA	16 ~ 32	_	_	VISA	A small molecule inhibitor of *Staphylococcus aureus*	2011[93]

Abbreviations: GISA, glycopeptide-intermediate *Staphylococcus aureus*; hVISA, hetero-vancomycin-intermediate *Staphylococcus aureus*; VISA, vancomycin-intermediate *Staphylococcus aureus*.

V outperform parental nisin against hVISA and hypervirulent pathogens, with broad-spectrum activity validated in food systems.[62] Additionally, synthetic amphiphilic dipeptides (eg, Trp-His(1-Bn)-NHBn) target fungal and bacterial membranes via charge-hydrophobicity interplay, though direct VISA data are pending.[94] Collectively, these peptides leverage membrane disruption, resistance evasion, and optimized pharmacokinetics to address VISA/hVISA infections across systemic, topical, and complex biofilm-associated contexts.

Synthetic Agents

Pyridyl disulfides exhibited high susceptibility against VISA/VRSA via 7–9 carbon alkyl chains, synergized with vancomycin, and disrupted biofilms.[63] Alpha-amyrin (AM) reduced biofilm biomass in clinical VISA isolates but increased metabolic activity, suggesting non-bactericidal effects.[64] Aryl-4-guanidinomethylbenzoate and N-aryl-4-guanidinomethylbenzamide derivatives showed MICs of 0.5–8 μg/mL against VISA, comparable to linezolid.[65] Benzoheptacyclic derivatives 48 and 51 inhibited staphyloxanthin biosynthesis by targeting CrtN, sensitized VISA strain Mu50 to hydrogen peroxide, and displayed efficacy comparable to linezolid in vivo.[66] 8-Hydroxycycloberberine derivative 15a achieved MIC of 0.25–0.5 μg/mL against VISA by suppressing topoisomerase IV.[67] Glycosylated lipo-vancomycin analogs exhibited 128–1024-fold enhanced activity against VISA compared to vancomycin, with optimized pharmacokinetics.[68] Retapamulin demonstrated MIC_{90} of 0.12 μg/mL against VISA/VRSA and remained active against 94% of mupirocin-resistant isolates.[70] Benzothiazole compound 7a exhibited in vivo efficacy in a VISA murine infection model.[71] Chroman/coumaran derivatives 69 and 105 potently inhibited virulence factors in VISA strain Mu50.[72] 1,4-Benzodioxane-derived inhibitor 47 showed anti-VISA activity comparable to linezolid in vivo.[73] Bis-indole derivatives displayed MIC of 1–4 mg/L against VISA and inhibited the NorA efflux pump.[74] Eremomycin aminoalkylamides 4a,b outperformed vancomycin against glycopeptide-resistant strains (including VISA).[75] 3-Substituted indoles inhibited VISA growth via nucleophilic addition mechanisms (MIC: 8–16 mg/L).[76] Myricetin combined with vancomycin/oxacillin reversed VISA resistance.[77] 9,10-Dihydroacridine derivatives disrupted VISA cell division by promoting FtsZ polymerization.[69] Thieno[2,3-d]pyrimidinediones achieved MIC of 2–16 mg/L against VISA/VRSA with low cytotoxicity.[78] These diverse synthetic agents, operating through distinct mechanisms, expand therapeutic strategies against multidrug-resistant staphylococcal infections.

Natural Derivatives

Recent advancements highlight the potential of naturally derived antimicrobial compounds as promising candidates against these multidrug-resistant strains, with several demonstrating efficacy in both in vitro and in vivo models. Plant-derived antimicrobial agents, such as Achyrofuran (a 2,2′-biphenol compound targeting membrane integrity),[79] Galangin (a flavonoid inhibiting peptidoglycan biosynthesis),[81] Anisochilus carnosus acetone extract (Acace, disrupting cell division),[85] exemplify diverse antibacterial mechanisms. Similarly, pterostilbene,[84] soybean glycinin basic subunit,[83] synergistic combinations like sodium new houttuyfonate with berberine chloride[88] and Valencia Orange Oil (CPV),[82] further underscore the versatility of phytochemicals in compromising bacterial survival through membrane permeabilization or metabolic interference. Meanwhile, microbially derived compounds, including bioactive metabolites from cyanobacteria[80] and Pseudomonas aeruginosa,[87] exhibit multifaceted antibacterial mechanisms, such as membrane destabilization, induction of oxidative stress, and metabolic inhibition. Semi-synthetic derivatives, such as the quercetin–pivaloxymethyl conjugate (Q-POM),[86] not only exhibit intrinsic antibacterial activity but also enhance the potency of conventional antibiotics (eg, vancomycin, ceftolozane-tazobactam), suppress biofilm formation, and delay resistance evolution. While many natural products show promising in vitro activity with low cytotoxicity, their clinical translation hinges on rigorous preclinical validation. Comprehensive studies are imperative to elucidate molecular mechanisms, optimize pharmacokinetic profiles, and evaluate long-term toxicity. Moreover, synergistic combination therapies—integrating natural compounds with existing antimicrobials—could amplify efficacy, reduce therapeutic doses, and circumvent resistance mechanisms. This strategy may prove pivotal in addressing multidrug-resistant infections and shaping the future of antimicrobial drug development.

Other

The "reverse antibiotic" nybomycin selectively targets quinolone-resistant VISA strains (eg, Mu50) by reverting gyrA mutations, restoring susceptibility to quinolones while exhibiting negligible resistance development (<1 × 10^{-11}/generation).[90] The cytotoxic nucleoside analog gemcitabine and its derivative CP-4126 inhibit VISA, MRSA, and MSSA (MIC 0.06–4.22 mg/L) via bactericidal synergy with gentamicin, with resistance linked to mutations in nucleoside kinase gene SadAK.[91] Telomycin, a phage-resistant Streptomyces-derived metabolite, exhibits potent activity against MRSA-VISA and Listeria monocytogenes, with antibacterial efficacy doubled in phage-resistant strains.[89] Targeting RNA degradation, a novel RnpA inhibitor suppresses mRNA/rRNA turnover in MRSA, VISA, and VRSA, demonstrating efficacy in systemic mouse infections and biofilm disruption.[93] Lastly, the folate synthesis inhibitor iclaprim suppresses Panton-Valentine leukocidin (PVL) and alpha-hemolysin (AH) toxin production in VISA and MRSA at sub-

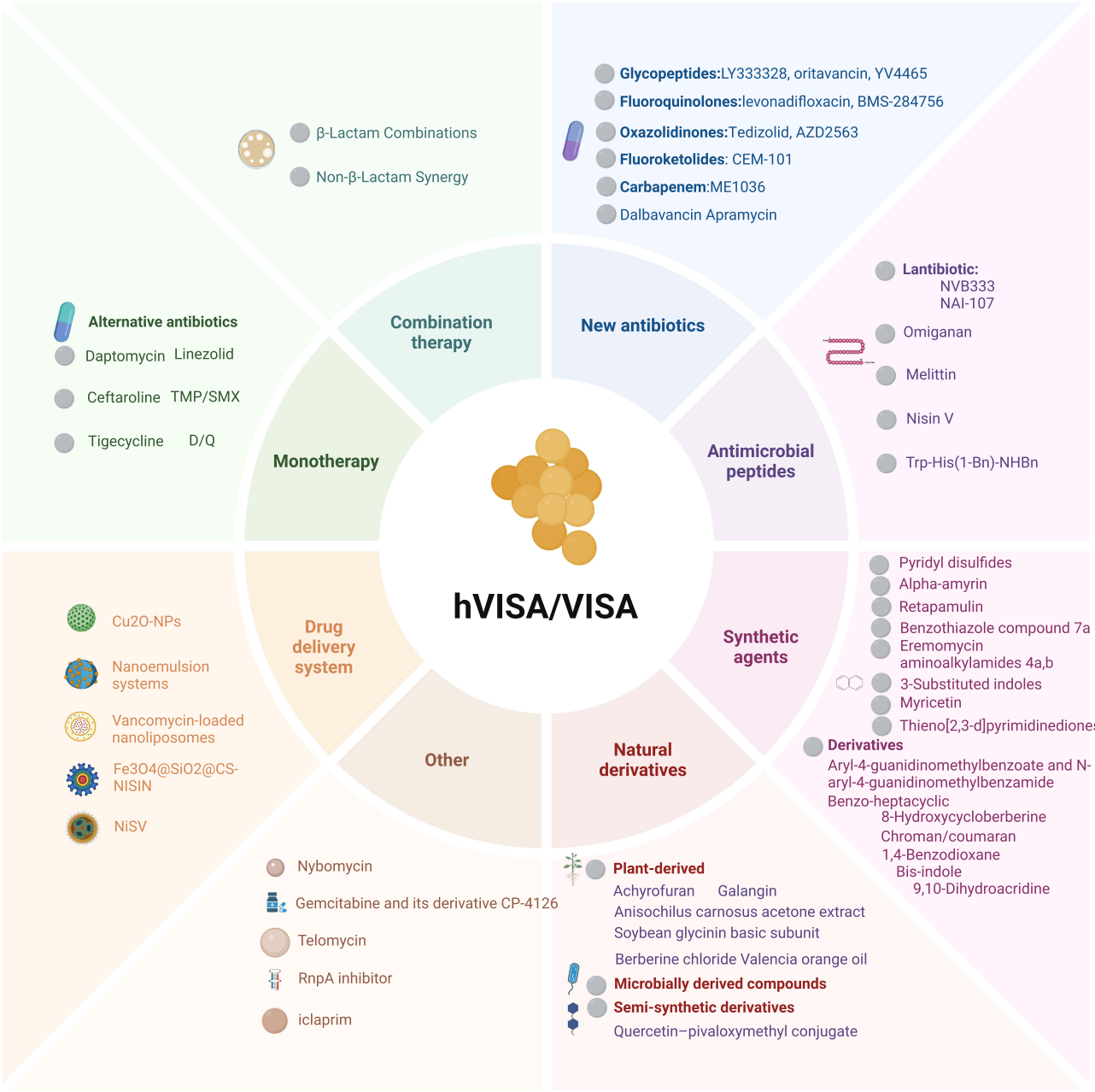

Figure 1 Summary of antimicrobial strategies against hVISA/VISA Created in BioRender. Cheng, X (2025) https://BioRender.com/2s04loo.

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MIC levels, outperforming trimethoprim and vancomycin in toxin suppression while concentrating at infection sites.[92] Collectively, these agents exploit resistance reversal (nybomycin), RNA catabolism (RnpA inhibitor), toxin modulation (iclaprim), and novel biosynthesis pathways (telomycin), offering multifaceted strategies to combat VISA/hVISA infections.

Drug Delivery System

In addition to the discovery of novel antimicrobial agents, improvements in drug delivery systems represent another direction. In recent years, drug delivery systems have shown great potential in treating hVISA and VISA. Copper(I) oxide nanoparticles (Cu2O-NPs), as a novel antimicrobial agent, significantly inhibited the growth of *Staphylococcus aureus* and effectively combated biofilm formation by disrupting bacterial cell membranes and causing leakage of cellular components, all while showing no cytotoxicity.[95] This makes them a promising candidate as an anti-biofilm agent in medical devices. Similarly, nanoemulsion systems, such as those containing cinnamon and clove oils, demonstrated high antimicrobial activity, particularly in nanoemulsions with Tween 20, which exhibited significant anti-biofilm effects (66–76%) and rapid bacterial membrane disruption, making them a powerful tool against VISA.[96] Additionally, vancomycin-loaded nanoliposomes enhanced drug stability and penetration, effectively lowering the MIC for resistant strains and preventing the development of vancomycin resistance, offering a new strategy to boost vancomycin efficacy.[97] Furthermore, magnetic nanocomposites (Fe3O4@SiO2@CS-NISIN) functionalized with nisin show excellent local antibacterial effects, effectively inhibiting hVISA and VISA growth and providing strong support for novel antimicrobial materials.[98] Finally, melittin (Mel)-loaded nonionic surfactant vesicles (NiSV) target bacterial membranes, disrupting membrane integrity and demonstrating significant antimicrobial activity against MRSA and VISA.[60] These systems significantly enhance therapeutic efficacy through several synergistic mechanisms, including improved drug bioavailability, spatiotemporally controlled release via pH/enzyme-responsive drug delivery, enhanced penetration of biofilm physical barriers, and multi-target antimicrobial actions such as membrane disruption, reactive oxygen species (ROS) generation, and metabolic interference. Together, these advancements lay a critical foundation for the development of next-generation intelligent antimicrobial agents, demonstrating substantial translational potential in addressing medical device-associated infections and persistent skin infections.

Conclusions

hVISA and VISA present significant clinical challenges. The emergence of these pathogens underscores the formidable obstacles facing conventional antibacterial therapies. This review consolidates all reported treatment strategies for hVISA and VISA since their identification, encompassing monotherapy, combination therapy, the development of novel antibacterial agents, and advanced drug delivery systems (Figure 1). While these interventions often demonstrate efficacy in vitro or in animal models, their clinical reliability remains unproven. Future research should prioritize: 1) elucidating the synergistic mechanisms of combination therapies and establishing standardized concentration-effect models; 2) designing highly selective drugs targeting specific hVISA/VISA molecular targets (eg, CrtN, FtsZ); 3) optimizing delivery systems for precise antibacterial action and resistance mitigation; 4) leveraging multi-omics approaches to inform personalized treatment regimens; and 5) accelerating the clinical translation of natural products and synthetic compounds. Furthermore, interdisciplinary efforts—such as AI-driven drug design and microbiome modulation—should be intensified to counter evolving resistance. These strategies offer a promising pathway to surmount current therapeutic limitations and deliver safer, more enduring solutions for multidrug-resistant Staphylococcus infections.

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Figure was created in https://BioRender.com and we have provided proof of the BioRender license to publish Figure 1.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing

the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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