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REVIEW ARTICLE**Clinical implications of vancomycin heteroresistant and intermediately susceptible*****Staphylococcus aureus***

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1 **Abstract.** *Staphylococcus aureus* has proven to be a major pathogen with the emergence of
2 methicillin-resistant *S. aureus* (MRSA) infections and recently with heteroresistant vancomycin
3 intermediate *S. aureus* (hVISA) and vancomycin intermediate *S. aureus* (VISA) infections. While
4 vancomycin is traditionally a first line and relatively effective antibiotic, its continued use is under
5 question, as reports of heteroresistance in *S. aureus* isolates are increasing. Both hVISA and VISA
6 infections are associated with complicated clinical courses and treatment failures. The prevalence,
7 mechanism of resistance, clinical significance, and laboratory detection of hVISA and VISA
8 infections are not conclusive, making it difficult to apply research findings to clinical situations.
9 We provide an evidence based review of *S. aureus* isolates expressing heterogenic and reduced
10 susceptibility to vancomycin.

11 **Introduction**

12 Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most commonly encountered bacteria
13 in hospitals and community settings¹ and is associated with invasive infections ranging in severity
14 from mild to fatal.² Vancomycin is considered the standard treatment for empiric and definitive
15 serious MRSA infections.² In recent years, infections caused by MRSA with reduced
16 susceptibility to vancomycin have emerged. The formation of intermediate resistant isolates is
17 likely caused by selection pressure from ever-present and longstanding use of vancomycin.³⁻⁵ Poor
18 patient outcomes are attributed to heteroresistant vancomycin intermediate *S. aureus* (hVISA) and
19 vancomycin intermediate *S. aureus* (VISA) infections.⁶⁻⁸ Herein we review the prevalence,
20 laboratory detection and interpretation, resistance mechanisms, risk factors and outcomes,
21 treatment options, and infection control strategies for hVISA and VISA. Peer-reviewed
22 publications were identified using PubMed, Embase, and Cochrane Central Register of Controlled
23 Trials.

24

25 **Prevalence of hVISA and VISA**

26 The first clinical strain of *S. aureus* with intermediate resistance to vancomycin, designated Mu50,
27 was reported in 1997 from Japan.^{9,10} The first hVISA isolate, designated Mu3, was identified in
28 Japan one year earlier from a patient with MRSA pneumonia unresponsive to vancomycin.⁹ Since
29 then, hVISA and VISA cases have been reported in the United States, United Kingdom, China,
30 Australia, Turkey, France, Belgium, Germany, Italy, Brazil, and South Korea.¹¹ The true
31 prevalence of hVISA is unknown, and estimates vary widely because of non-standardized
32 detection methodologies or absence of routine hVISA screening, variation in interpretation,

33 geographical location, clinical setting, and differing patient populations.¹²⁻¹⁹ Reported rates of
34 hVISA throughout the world range from 0 to 73.7%.¹⁸

35

36 One retrospective study evaluated MRSA strains with heterogenic intermediate resistance to
37 vancomycin over a 22-year period in three Detroit hospitals. The prevalence of these organisms
38 increased from 2.2% (1986 – 1993) and 7.6% (1992 – 2002) to 8.3% between 2003 and 2007.¹⁶

39 Only 14 of the 1,498 (0.93%) MRSA isolates were identified as VISA. There was no apparent
40 pattern of increasing prevalence over the three time periods for VISA isolates. An increase in
41 hVISA was also described in a similar retrospective study from Turkey of 1.6% in 1998 to 36%
42 in 2001.²⁰ Because clonality was not evaluated in either study, the increase in prevalence may

43 have reflected clonal spread rather than true prevalence. Prevalence may have been
44 underestimated because the isolates were stored for prolonged periods in glycopeptide-free media,
45 which may result in a loss of resistance.²¹ Two surveillance studies conducted in 2009 and 2011

46 in over 40 U.S. medical centers determined rates of antimicrobial resistance among *S. aureus*
47 isolates collected from patients with infections.^{22,23} The rates of hVISA among MRSA isolates in
48 2011 were higher than in 2009 (1.2% vs. 0.4%, $P = 0.003$).²² Of note, strains of VISA were not

49 detected.^{22,23} While the current prevalence of VISA is low, these organisms may become more
50 common in the future. Data suggests that heteroresistance is a precursor to VISA, therefore the
51 suspected increase in prevalence of hVISA may predict more VISA infections. Increased use of

52 vancomycin provides selection pressure for further emergence of VISA. Based on available data,
53 hVISA appears to be on the rise, yet VISA still remains a rare occurrence. Additional studies are
54 needed to determine appropriate surveillance methods because retrospective studies are

55 complicated by the ability of hVISA to revert back to vancomycin-susceptible *S. aureus* (VSSA)
56 and VISA to revert back to hVISA.

57

58 **hVISA and VISA Laboratory Detection and Interpretation**

59 Further discussion of hVISA and VISA require that clinical and microbiologic definitions are
60 addressed. In 2006, the Clinical and Laboratory Standards Institute (CLSI) lowered vancomycin
61 minimum inhibitory concentration (MIC) breakpoints for *S. aureus*.²⁴ The CLSI breakpoints by
62 broth microdilution (BMD) currently define vancomycin susceptibility as an MIC ≤ 2 $\mu\text{g/mL}$,
63 vancomycin-intermediate susceptibility as an MIC of 4 to 8 $\mu\text{g/mL}$, and vancomycin resistance as
64 an MIC of ≥ 16 $\mu\text{g/mL}$ (**Table 1**).²⁵ Vancomycin MIC breakpoints were lowered in an effort to
65 increase detection of potentially heterogeneous-intermediate isolates because of reported
66 associations between vancomycin treatment failure and *S. aureus* isolates with MICs ≥ 4
67 $\mu\text{g/mL}$.^{7,8,25} Heteroresistance refers to the presence of less susceptible subsets within a larger
68 population of fully antimicrobial-susceptible microorganisms.⁵ When tested using routine
69 methods, hVISA isolates are susceptible to vancomycin (MIC ≤ 2 $\mu\text{g/mL}$) but contain
70 subpopulations that express reduced vancomycin susceptibility (MIC ≥ 4 $\mu\text{g/mL}$).¹¹

71

72 Detection of hVISA is a great challenge in clinical microbiology laboratories because reliable and
73 practical methods are not currently available for routine use. Heteroresistant subpopulations are
74 present in low frequencies ($\geq 1 \times 10^6$) and can grow in higher vancomycin concentrations than the
75 MIC predicts. Such small populations may not be detected by the inocula (5×10^5 CFU/mL)
76 used in standard CLSI microbiology methods. As a result, hVISA isolates are likely undetected
77 in clinical laboratories that use traditional MIC testing methodology.¹³ Population analysis

78 profiling with area under the curve (PAP-AUC) is the current reference standard method for
79 confirming hVISA and is the most reliable and reproducible test. However PAP-AUC is labor-
80 intensive, time consuming (3 to 5 days), and costly for use in clinical microbiology
81 laboratories.^{17,19,26} Consequently, several screening methods have been developed, such as
82 glycopeptide resistance detection (GRD), marcomethod E-test (MET) and brain heart infusion
83 (BHI) screen agar plates (**Table 2**).²⁷⁻²⁹ However, none of these tests have the same degree of
84 sensitivity and specificity as the PAP-AUC test, with issues of reproducibility and variability, in
85 reporting results.¹⁹ Until a suitable hVISA detection method becomes available for use in clinical
86 microbiology laboratories, routine testing is not currently recommended.² Currently, clinical
87 screening for hVISA isolates in high-risk patients is favored (**Table 3**), particularly in patients who
88 do not respond to vancomycin. Further research is warranted to develop a detection method that
89 is practical, cost-effective, and reliable for routine use in clinical settings.

90

91 Non-automated MIC methods for the detection of VISA are recommended by the Centers for
92 Disease Prevention and Control (CDC).³⁰ Acceptable non-automated MIC methods for detecting
93 VISA include BMD per CLSI, agar dilution, and Etest (0.5 McFarland).³⁰ Though automated
94 methods and vancomycin screen agar plates can be useful in the detection of VISA isolates with a
95 vancomycin MIC of 8 µg/mL, sensitivity levels have not been determined for *S. aureus* with
96 vancomycin MICs of 4 µg/mL.³⁰ In these situations, a second method, such as BMD per CLSI
97 criteria, should be used to confirm VISA isolates.³⁰

98

99 Current susceptibility testing methods do not consistently distinguish between MICs of 1 and 2
100 µg/mL.^{2,31} Therefore, laboratory results should indicate the methodology used, because

101 vancomycin MIC results will differ between methods and may alter treatment decisions.¹¹ In
102 comparison to the CLSI BMD method, automated detection methods, particularly Phoenix system
103 and Vitek, tend to underestimate the MIC, while E-test and MicroScan (prompt method) may
104 overestimate the MIC.³¹ Precision of these methods is clinically important as higher vancomycin
105 MICs ($> 1.5 \mu\text{g/mL}$) are associated with poorer outcomes (e.g., increased mortality, recurrence,
106 delayed response, treatment failure, prolonged hospitalization), particularly in high inoculum
107 infections and with a higher proportion of hVISA presence.^{25,32} Alternative therapies should be
108 considered for patients receiving vancomycin therapy who are persistently bacteremic (≥ 7 days)
109 or who have no clinical improvement despite source control with an MIC of $\geq 1.5 \mu\text{g/mL}$ by
110 Etest.^{2,31,32}

111

112 **Resistance Mechanisms of hVISA and VISA**

113 Evidence suggests that hVISA and VISA arise during continued or sub-optimal exposure to
114 vancomycin.^{7,33} The proposed mechanism is selective pressure by vancomycin resulting in the
115 development of rare vancomycin-resistant clones that progress to hVISA and, with continued-
116 exposure, to a uniform population of VISA clones.^{5,9} These isolates have significant differences
117 in cell physiology, including morphologic changes and genetic alterations. Strains of hVISA and
118 VISA are characterized by thicker cell walls that correlate with increased vancomycin MICs.³⁴
119 Cell wall thickening impairs intracellular penetration of vancomycin rendering it ineffective.^{5,34}
120 In addition, hVISA and VISA are associated with slower growth rates than fully susceptible
121 strains, which may contribute to persistent and recurrent infections.³⁵ Other mechanisms of
122 resistance include alterations in transcriptional and metabolic genes and loss-of-function mutations
123 that disturb critical cell wall biosynthesis.¹¹ The accessory gene regulator (*agr*) operon directs

124 many critical virulence pathways, particularly the production of exotoxins.¹¹ In hVISA and VISA
125 strains, *agr* function is reduced, favoring the development of vancomycin resistance and
126 potentially promoting biofilm production that ultimately enhances the survival of hVISA and
127 VISA.^{33,36,37}

128

129 **Risk Factors and Outcomes Associated with hVISA and VISA**

130 Heteroresistance has been reported in MRSA isolates with MICs as low as 0.5 µg/mL and in cases
131 where vancomycin was minimally effective.^{6,16} Several studies have noted an increase in
132 vancomycin treatment failures and mortality with vancomycin susceptible MRSA strains,
133 particularly those with MICs of 1.5 or 2 µg/mL.^{25,32,38-40} A recent meta-analysis of 20 studies
134 evaluated high versus low vancomycin MICs (≥ 1.5 µg/mL vs < 1.5 µg/mL, respectively) on
135 clinical outcomes in adults with MRSA infections.⁴⁰ An increased risk of failure was observed in
136 the high MIC group compared to the low MIC group (relative risk [RR], 1.40; 95% confidence
137 interval [CI], 1.15 – 1.71). There was also a greater risk of overall mortality (RR, 1.45; 95%
138 CI, 1.08-1.87) in the high MIC group. Although the investigators attempted to exclude hVISA
139 isolates, hVISA presence was not tested in every study, which may have contributed to
140 vancomycin treatment responses. While most of the isolates were from blood, clinical
141 heterogeneity cannot be excluded. Another study evaluated 559 MRSA isolates and found an
142 increased incidence of hVISA when the vancomycin MIC shifted from 1 to 2 µg/mL.⁴¹ The
143 incidence of hVISA was nearly 40% in isolates with an MIC of 2 µg/mL, supporting the results of
144 other studies that suggest the proportion of hVISA isolates are directly related to increases in
145 vancomycin MIC.^{6,15,23,41} Increases in vancomycin MICs are hospital specific and perhaps caused
146 by clonal outbreaks. However, this highlights the trends of vancomycin tolerance, which may be

147 caused by overuse of vancomycin, sub-therapeutic vancomycin concentrations, high bacterial load,
148 or slow vancomycin bactericidal activity.^{3,42}

149

150 Both hVISA and VISA have been identified in hospital and community strains of MRSA and in
151 MSSA.¹⁶ The findings of studies that evaluated clinical predictors and outcomes of hVISA
152 infections are inconsistent. This may be attributed to the considerable heterogeneity of these
153 studies, including differences in study design, clinical definitions, selection of isolates (initial
154 isolate, final isolate, or random selection), patient populations, and testing methodologies.
155 Commonly reported associations with hVISA infections include vancomycin treatment failure and
156 high-inoculum MRSA infections (e.g., bacteremia, infective endocarditis, osteomyelitis, deep
157 abscesses, and prosthetic device infections).^{6,7,14,33,43,44} Other potential predictors of hVISA and
158 VISA infections are prior MRSA infection or colonization (previous 3 months), previous
159 vancomycin exposure (prior 6 months), initial low serum vancomycin trough levels ($< 10 \mu\text{g/mL}$),
160 persistent bacteremia (≥ 7 days), and presence of indwelling devices (**Table 2**).^{7,8,12,14,44,45 46}

161

162 Patients with hVISA infections tend to experience prolonged clinical courses, suboptimal response
163 to vancomycin therapy, and prolonged hospital stays.^{6-8,14,33,42,44} One retrospective case-control
164 study compared the clinical features and outcomes of hVISA bacteremia ($n = 27$) and MRSA
165 bacteremia ($n = 223$).¹⁴ Compared with MRSA bacteremia, patients with hVISA infections had
166 significantly more days of bacteremia (median duration, 12 days vs. 2 days, respectively; $P =$
167 0.005) and significantly higher rates of endocarditis (18.5% vs. 3.6%, respectively; $P = 0.007$) and
168 osteomyelitis (25.9% vs. 7.2%, respectively; $P = 0.006$).¹⁴ Of note, patients in the hVISA group
169 had significantly more prosthetic/implant devices (e.g., artificial heart valves, pacemakers, or

170 orthopedic implants) and surgical site infections (in the previous month) at baseline, which may
171 have attributed to poorer outcomes. In a small case series, glycopeptide treatment failure, (defined
172 as a positive *S. aureus* blood culture after ≥ 7 days of glycopeptide therapy or a sterile site culture
173 positive for *S. aureus* after ≥ 21 days of glycopeptide therapy) occurred in 19 of 25 (76%) patients
174 with hVISA infections (bacteremia, endocarditis, osteomyelitis, or septic arthritis).⁸

175
176 A retrospective, multicenter, matched cohort study compared the outcomes of hVISA versus
177 vancomycin susceptible-MRSA (VS-MRSA) bloodstream infections (BSI) and found similar
178 results.⁶ Study investigators concluded that rates of vancomycin treatment failure were 11 times
179 higher for a patient with hVISA BSI (50/61, 82%) than VS-MRSA BSI (20/61, 32.8%; $P < 0.001$).
180 Patients with hVISA BSI were also more likely than patients with VS-MRSA BSI to have
181 persistent bacteremia (59% vs. 21.3%, respectively; $P < 0.001$), infection recurrence at 60 days
182 (25.5% vs. 1.9%, respectively; $P < 0.001$), and longer hospital length of stay (median in days, 24
183 vs. 16, respectively; $P = 0.022$). While differences in 30-day MRSA infection-related mortality
184 and all-cause 30-day mortality were not observed between the hVISA BSI group and VS-MRSA
185 BSI group (21.3% vs. 9.8%; $P = 0.081$ and 24.6% vs. 11.5%; $P = 0.076$, respectively). Similarly,
186 no other studies have been powered to detect a significant difference in mortality between hVISA
187 and non-hVISA infections. A recent systematic review and meta-analysis evaluated 30-day
188 mortality from eight comparative hVISA studies.¹⁸ After combining the data, 30-day mortality
189 between hVISA and VSSA infections were similar (OR, 1.18; 95% CI, 0.81-1.74).¹⁸ However,
190 these findings may be limited by the variability in definitions used and the predominately
191 retrospective designs of the original studies. While the lack of association between hVISA and
192 mortality can be partly explained by strain characteristics (e.g., decreased virulence) and host

193 immune responses, sufficiently sized studies are needed to accurately determine if such an
194 association exists.⁴⁷

195
196 Infections caused by VISA may also lead to recurrent infections, prolonged fevers and bacteremia,
197 vancomycin treatment failure, and increased hospital stay.^{7,12,33,44} In a single-center, retrospective
198 study, 6 patients with VISA had a significantly longer duration of bacteremia compared to 22 with
199 hVISA (12.1 ± 13.1 days vs. 3.3 ± 3.9 days, respectively; P = 0.001).⁴³ Significant differences in
200 mortality between VISA and hVISA were not observed. However, rates of attributable mortality
201 between hVISA and VSSA (n = 215) were similar (9.1% vs. 8.4%, respectively) while those
202 between VISA and VSSA (33.3% vs. 8.4%) were not.⁴³ Although this study had several
203 limitations including a small sample size and bias through selective inclusion of isolates, the
204 findings suggest that VISA may have more severe clinical implications and impact on patient
205 outcomes. To date, no other published study has evaluated the outcomes of VISA infections,
206 possibly because of the rarity of VISA infections.

207

208 **Treatment Options for hVISA/VISA Infections**

209 Although reports of vancomycin failure have emerged, no data demonstrate superior outcomes
210 with alternative antimicrobials. Alternative antimicrobial agents with activity against
211 hVISA/VISA include daptomycin, linezolid, ceftaroline, trimethoprim/sulfamethoxazole,

212 tigecycline, quinupristin/dalfopristin, and the combination of vancomycin or daptomycin with a
213 beta-lactam.¹²

214

215 Daptomycin

216 Daptomycin is a potential treatment option for hVISA and VISA infections and, although it does
217 have activity against MRSA, previous vancomycin exposure can result in some degree of cross-
218 resistance to daptomycin.^{48,49} Several studies have noted an *in vitro* association between
219 increasing vancomycin MICs and increasing daptomycin non-susceptibility.⁴⁸⁻⁵⁰ The highest rate
220 of daptomycin non-susceptibility was reported in a study evaluating 47 Australian hVISA and
221 VISA isolates never exposed to daptomycin.⁵⁰ The investigators noted daptomycin non-
222 susceptibility in 15% of hVISA and 38% of VISA strains.⁵⁰ Because bactericidal activity with
223 daptomycin is concentration dependent, higher doses may be necessary to treat hVISA and VISA
224 infections with elevated daptomycin MICs, high inoculum infections (e.g., endocarditis), and
225 infection sites characterized by poor antimicrobial penetration.⁵¹ High-dose daptomycin may
226 prevent the selection or development of isolates with reduced susceptibility to daptomycin and
227 subsequent treatment failure.⁵¹

228

229 An *in vitro* study observed more rapid reduction of bacterial burden of hVISA and VISA in
230 simulated endocardial vegetations with high-dose daptomycin (10 mg/kg/day for 8 days) and dose
231 de-escalation (10 mg/kg/day for 4 days followed by 6 mg/kg/day for 4 days) regimens compared
232 to that of the standard (6 mg/kg/day for 8 days) and dose escalation (6 mg/kg/day for 4 days
233 followed by 10 mg/kg/day for 4 days) regimens.⁵¹ With respect to hVISA, the dose de-escalation
234 regimen had a significantly increased killing effect on the hVISA strain compared to the dose

235 escalation regimen ($P < 0.024$).⁵¹ The investigators concluded that these daptomycin dosing
236 approaches may lead to a faster cure of bacteremia *in vivo* and prevent the emergence of
237 daptomycin non-susceptibility.⁵¹ However, no *in vivo* studies evaluating de-escalation dosing and
238 the appropriate duration of high-dose daptomycin have been published. The role of high-dose
239 daptomycin alone in patients with hVISA or VISA infections is unclear. Until more evidence is
240 available, caution is required when considering daptomycin in patients who may be at risk for
241 hVISA or VISA infections (e.g. high-bacterial load infections, vancomycin failure). The
242 determination of daptomycin susceptibility in these patients may also guide therapeutic decision
243 making.

244

245 Linezolid

246 The role of linezolid for the treatment of invasive hVISA and VISA infections is also in question.
247 Successful use of linezolid alone or in combination with other antimicrobial agents has been
248 described in several case reports of vancomycin heteroresistant and intermediate MRSA
249 endocarditis and bacteremias after vancomycin failure and in some cases after daptomycin
250 failure.^{8,52-55} In one case report, a 60 year old male with an automatic implantable cardioverter-
251 defibrillator (AICD) presented with bacteremia and endocarditis initially caused by MRSA which
252 later developed into hVISA, then daptomycin non-susceptible VISA after exposure to vancomycin
253 and daptomycin.⁵⁵ The patient initially received 6 weeks of vancomycin (trough concentrations
254 between $\geq 15 \mu\text{g/mL}$ and $\leq 21 \mu\text{g/mL}$), followed by approximately 25 days of daptomycin (6
255 mg/kg every 48 hours, renal dose adjusted). During therapy with daptomycin the defibrillator
256 generator and leads were removed however, the patient was persistently bacteremic and febrile.
257 Blood cultures cleared after therapy was switched to linezolid and trimethoprim/sulfamethoxazole.

258 The patient received at least 28 days of the combination and 6 weeks of linezolid monotherapy in
259 total since the last positive blood culture. One year post-treatment the patient had no infection
260 recurrence. After failing vancomycin and daptomycin therapy, this patient's VISA infection was
261 successfully treated with linezolid. While other case reports have shown similar outcomes with
262 the use of linezolid, *in vitro* studies have not shown the same efficacy.⁵⁶ Evidence to recommend
263 the use of linezolid for hVISA and VISA is insufficient. Further study is needed to evaluate
264 linezolid alone or in combination for hVISA and VISA infections.

265

266 Ceftaroline

267 Ceftaroline has potent *in vitro* bactericidal activity against MRSA including hVISA, VISA, and
268 daptomycin non-susceptible (DNS) MRSA strains.⁵⁷ The use of ceftaroline in the treatment of
269 invasive infections (e.g., endocarditis, bacteremia, osteomyelitis) caused by hVISA, VISA, and
270 DNS MRSA is supported by data from *in vivo* animal studies and human case reports.⁵⁸⁻⁶¹ In a
271 recent case series report, a patient with DNS VISA bacteremia and endocarditis was successfully
272 treated with 6 weeks of ceftaroline. The patient initially received and failed vancomycin therapy.⁶²
273 Blood cultures cleared within 48 hours of switching to daptomycin (6 mg/kg/day). However,
274 subsequent blood cultures were positive and revealed DNS VISA. Daptomycin was discontinued,
275 and ceftaroline (600 mg IV every 8 hours) was initiated. While on ceftaroline, blood cultures
276 cleared within 48 hours and remained sterile. *In vitro* pharmacokinetic/pharmacodynamic studies
277 reported enhanced ceftaroline activity against hVISA, VISA, and DNS MRSA as vancomycin and
278 daptomycin susceptibilities decreased, which have been referred to as the "seesaw effect".⁵⁸⁻⁶⁰
279 While further study is needed, ceftaroline appears to be a safe and effective alternative in the

280 treatment of invasive hVISA, VISA, and DNS MRSA infections given its bactericidal activity,
281 favorable safety profile, and emerging data.

282

283 Combination therapy

284 The combination of vancomycin or daptomycin and a beta-lactam antimicrobial has also been
285 studied for treatment of hVISA and VISA infections. Beta-lactams that have been evaluated for
286 synergistic activity with vancomycin or daptomycin include ceftaroline, cefazolin, and
287 piperacillin-tazobactam.⁶³⁻⁶⁶ *In vitro* and clinical case report data evaluating the combination of
288 high-dose daptomycin (10 mg/kg/day) and trimethoprim/sulfamethoxazole also appear promising
289 for the treatment of hVISA, VISA, and DNS MRSA infections.^{67,68} *In vitro* studies have
290 demonstrated improved kill rates with these antimicrobial combinations.⁶³⁻⁶⁵ Investigators
291 hypothesize that beta-lactam exposure may influence vancomycin-cell wall interactions to
292 improve vancomycin activity, although further investigation is warranted.⁶³ In summary,
293 preliminary experimental studies show possible prospects for the treatment of hVISA and VISA
294 infections. However, it is not yet clear which treatment options correlate with optimal clinical
295 outcomes for patients with confirmed hVISA or VISA infections.

296

297 **Infection Control: Preventing the Dissemination of hVISA/VISA**

298 As with MRSA, hVISA and VISA can colonize humans and the environment despite eradication
299 efforts. The CDC has made several recommendations in an attempt to prevent the emergence of
300 vancomycin non-susceptible infections.⁴² Infections with confirmed VISA should be reported to
301 infection-control personnel, the patient's primary caregiver, medical ward staff, local and state
302 departments of health, and the CDC. Patients and their caregivers should be educated regarding

303 wound care, physical hygiene, and signs of infection.⁶⁹ Contact isolation in both the inpatient and
304 outpatient setting may also limit further emergence. Adherence to recommended infection
305 prevention and control guidelines, appropriate antibiotic prescribing through antimicrobial
306 stewardship programs, and active surveillance in a cohesive health care system are essential to
307 prevent further emergence of hVISA and VISA colonization and infection.

308

309 **Conclusions**

310 The evolution of *S. aureus* to MRSA and now to hVISA and VISA is an important and ongoing
311 public health concern. Vancomycin is the drug of choice for invasive MRSA infections, however,
312 its use is under question. Over-use, suboptimal concentrations, or inappropriate use of vancomycin
313 is speculated to be a major contributor in the emergence of hVISA and VISA. Most alarming are
314 the poor outcomes that have been associated with hVISA and VISA infections and the limited
315 antimicrobials available to treat these infections. Proper detection methods are necessary for
316 accurate surveillance, guidance on therapeutic decision-making, and a full understanding of the
317 implications of hVISA/VISA infections. Until then, patients who are at risk for hVISA/VISA
318 infections and failing vancomycin therapy may warrant further confirmatory testing for
319 hVISA/VISA. Based on currently available data, clinicians should, with vigilance, continue to use
320 vancomycin per the Infectious Diseases Society of America guidelines.^{2,3} Alternative therapies
321 should be considered in patients with risk factors for hVISA/VISA who are not responding
322 clinically to vancomycin despite source control and a vancomycin MIC ≤ 2 $\mu\text{g/mL}$. In patients
323 infected with VISA (vancomycin MIC 4 – 8 $\mu\text{g/mL}$), an alternative antimicrobial should be
324 considered. Caution is advised when deciding to use daptomycin in patients with hVISA/VISA

325 infections because of the potential for cross-resistance. To prevent further resistance, appropriate
326 use of antimicrobials and implementation of infection-control guidelines are imperative.

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Table 1. CLSI susceptibility definitions for vancomycin^{24,25}

	2006 CLSI Update MIC	Previous CLSI Breakpoints MIC
VSSA	$\leq 2 \mu\text{g/mL}^{\text{a}}$	$\leq 4 \mu\text{g/mL}$
VISA	4 – 8 $\mu\text{g/mL}$	8 – 16 $\mu\text{g/mL}$
VRSA	$\geq 16 \mu\text{g/mL}$	$\geq 32 \mu\text{g/mL}$

CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration;

VISA = vancomycin intermediate *S. aureus*; VRSA = vancomycin resistant *S. aureus*; VSSA = vancomycin susceptible *S. aureus*;

^a May contain heteroresistant intermediate susceptible subpopulations with MIC > 4 $\mu\text{g/mL}$. Heteroresistant vancomycin intermediate *S. aureus* (hVISA) isolates are not identified by CLSI and can occur at vancomycin MICs as low as 0.5 $\mu\text{g/mL}$.

Table 2. Advantages and disadvantages of laboratory detection methods for hVISA

Confirmatory Methods		
Method	Advantages	Disadvantages
PAP ^{4,11,13,26,70}	<ul style="list-style-type: none"> • Considered the “gold standard” • High reproducibility and accurate detection • Definitive confirmation: Modified PAP 	<ul style="list-style-type: none"> • No data to show superiority to other techniques • High labor intensity • High-cost • Long turn-around time
Screening Methods		
Method	Advantages	Disadvantages
GRD E-test (AB Biodisk) ^{17,19,27}	<ul style="list-style-type: none"> • Results ready to read following 24 hours of incubation • Uses standard bacterial inoculum 	<ul style="list-style-type: none"> • Unreliable specificity and sensitivity
MET or High inoculum method ^{11,29}	<ul style="list-style-type: none"> • 100% reproducibility • Easily performed 	<ul style="list-style-type: none"> • Testing performed on nonstandard media while utilizing a standard McFarland suspension • Results of MET are cut-off points, not true MICs
BHI screen agar plates ^{7,17,28}	<ul style="list-style-type: none"> • Easily performed 	<ul style="list-style-type: none"> • Poor reproducibility • Many variations; some studies screened with a different agar, inoculum size, or used suspensions with higher bacterial concentration

BHI = Brain Heart Infusion; GRD = Glycopeptide Resistance Detection; MET = Macromethod E-Test; MIC = minimum inhibitory concentration; PAP = Population Analysis Profiling

Table 3. Predictors and outcomes of hVISA and VISA

Predictors	Outcomes
<ul style="list-style-type: none"> • Previous vancomycin use • Prior MRSA infection or colonization • High bacterial load infections^a • Persistent bacteremia • Initially low serum vancomycin levels (<10 µg /mL) • Presence of indwelling devices 	<ul style="list-style-type: none"> • Long duration of bacteremia, days • Persistent fever • Recurrent infections • Vancomycin treatment failure • Prolonged hospitalization

hVISA = heteroresistant vancomycin intermediate *S. aureus*; MRSA = methicillin resistant *S. aureus*; VISA = vancomycin intermediate *S. aureus*

^aE.g.bacteremia, endocarditis, osteomyelitis, deep abscess, or prosthetic joint infection