Published in final edited form as:

Diagn Microbiol Infect Dis. 2009 October ; 65(2): 180–183. doi:10.1016/j.diagmicrobio.2009.05.017.

Clinical failure of vancomycin in a dialysis patient with methicillin-susceptible vancomycin-heteroresistant *S. aureus*★

Dahlene N. Fusco^{a,1}, Elizabeth L. Alexander^{a,1}, Scott A. Weisenberg^a, Jose R. Mediavilla^c, Barry N. Kreiswirth^c, Audrey N. Schuetz^b, Stephen G. Jenkins^b, and Kyu Y. Rhee^{a,*}

^aDivision of Infectious Diseases, Weill Cornell Medical College, New York Presbyterian Hospital, New York, New York 10065, USA

^bDepartment of Pathology and Laboratory Medicine, Weill Cornell Medical College, New York Presbyterian Hospital, New York, New York 10065, USA

^cPublic Health Research Institute Center, University of Medicine and Dentistry of New Jersey, Newark, New Jersey 07103, USA

Abstract

We report a case of recurrent *Staphylococcus aureus* bacteremia in a patient who failed vancomycin due to a vancomycin-heteroresistant strain lacking methicillin resistance. Although initial isolates were susceptible, isolates obtained after vancomycin chemotherapy were vancomycin heteroresistant. This case thus illustrates the clinical emergence of vancomycin heteroresistance.

Keywords

Vancomycin; Heteroresistance; Failure; *Staphylococcus aureus*

1. Introduction

Staphylococcus aureus is a major human pathogen and growing clinical challenge (Fowler et al., 2005). A major contributing factor to the clinical impact of *S. aureus* has been the rapid emergence of antibiotic resistance. Since the introduction of penicillin in 1942, *S. aureus* has developed resistance to every β -lactam-type antibiotic introduced to clinical medicine. Recent reports of heteroresistance to the glycopeptide antibiotic, vancomycin, are thus of considerable concern (Hiramatsu et al., 1997).

Vancomycin-heteroresistant *S. aureus* (hVISA) isolates are defined as *S. aureus* isolates for which the in vitro vancomycin MIC is less than 4 μ g/mL but contain subpopulations (typically at a rate of 1 in 10^5 to 10^6 organisms) with intermediate-level resistance to

★Portions of this manuscript have been submitted in abstract form for presentation at the American Society of Microbiology meeting in 2009.

¹Supported by T32 AI 007613 from the National Institutes of Health.

*Corresponding author. Division of Infectious Disease, Weill Cornell Medical College, New York, NY 10065, USA. Tel.: +1-212-746-4547; fax: +1-212-746-8675. kyr9001@med.cornell.edu (K.Y. Rhee).

vancomycin (Charles et al., 2004). hVISA isolates have been increasingly reported in association with methicillin-resistant *S. aureus* (MRSA) and higher rates of clinical failure (Charles et al., 2004). The scope and significance of such isolates, however, remains incompletely defined.

We report a case of recurrent methicillin-susceptible *S. aureus* (MSSA) bacteremia and vancomycin treatment failure that was associated with the development of vancomycin heteroresistance. This case provides a little-described window into the emergence of vancomycin heteroresistance and a clinical warning that the risk of failure of vancomycin may be greater than previously believed.

2. Case description

A 64-year-old woman with end-stage renal disease (on hemodialysis) and prior MRSA bacteremia (treated with vancomycin) was hospitalized with severe bilateral hip pain. Workup revealed septic arthritis of both native hips, and bilateral hip debridement was performed. Cultures of the hip aspirates and debrided material yielded MSSA. Because of a penicillin allergy, the patient was treated with vancomycin. Blood cultures taken 24 h after initiation of vancomycin revealed MSSA bacteremia, which persisted until her dialysis catheter was removed 4 days later. A transesophageal echocardiogram showed no evidence of valvular insufficiency or vegetation, and she was discharged to complete a course of vancomycin.

After discharge, the patient did well, with no recurrence of fevers and slow improvement of bilateral hip pain while receiving vancomycin at dialysis thrice weekly for 4 weeks. Serum vancomycin trough levels during this period were maintained in the range of 13 to 29 µg/mL, and weekly surveillance blood cultures remained negative.

During week 4 of vancomycin therapy, the patient noted recurrent pain in her left hip and new lower back pain. Spine and pelvic magnetic resonance imaging revealed a new L3 through L4 discitis and a new left hip effusion, and an indium-labeled leukocyte scan showed increased uptake in both the hip and spine. In addition, blood cultures again yielded MSSA. The patient underwent repeat debridement of the left hip and continued on vancomycin at the same intravenous dose, with subsequent clearance of blood cultures.

3. Results

Review of Vitek (bioMérieux, Durham, NC) antimicrobial susceptibility testing results for all *S. aureus* cultures revealed several discrepancies. First, the vancomycin MIC of 1 blood culture isolate (B1) from the initial presentation was 2 µg/mL, whereas all other isolates (3 sets of blood cultures [B2–B4] and 8 hip cultures [H1–H8]) were highly susceptible to vancomycin (MICs ≤ 1 µg/mL). Second, although all isolates associated with the patient's relapse remained vancomycin susceptible, the vancomycin MICs of these blood culture isolates (B5–B8) were 2 µg/mL, the Clinical and Laboratory Standards Institute upper limit of susceptibility (Sakoulas and Moellering, 2008). A timeline of the patient's clinical course summarizing the microbiologic characteristics of these isolates is presented in Fig. 1. All isolates tested susceptible to oxacillin (Fig. 1A) and lacked the *mecA* gene cassette by

targeted *mecA* PCR, (Rossney et al., 2008). Pulsed-field gel electrophoresis and spa typing confirmed the clonal relationship of all infecting *S. aureus* isolates (clonal complex ST45) (Fig. 1B) (Mulver et al., 2001). Taken together, these results established the patient's recurrent infection as a microbiologic failure while on appropriate doses of vancomycin.

To explore a role for vancomycin heteroresistance in the patient's treatment failure, MIC by broth microdilution, standard Etest, minimum bactericidal concentrations (MBCs), 0.5-McFarland Etest GRD strip, and population analysis profiling assays were also performed. For all studies, ATCC reference MSSA 29213 was used as a negative control, with reference hVISA Mu3 as a positive control. Etest GRD strip testing was performed according to the manufacturer's instructions using 100 μ L of a 0.5-McFarland suspension on Mueller–Hinton agar + 5% blood. Results were read after 24 and 48 h of incubation (Bernard et al., 2004; Rybak et al., 2008; Yusof et al., 2008).

As shown in Fig. 1A, vancomycin MICs and MBCs for all strains were 2 and >32 μ g/mL, respectively. By both standard Etest and Etest GRD strip testing, however, there was a notable increase in values, such that only the last isolate met the criteria by Etest GRD strip for heteroresistance (values >8 for both vancomycin and teicoplanin or >12 for teicoplanin alone). These results were confirmed by population analysis profiling-area under the curve (PAP-AUC), which demonstrated an expansion of resistant subpopulations as reported by PAP-AUC ratios (with only isolate B5 showing a PAP-AUC 0.9 versus Mu3) (Wootton et al., 2007).

Based on these results, the patient underwent immunologic desensitization to oxacillin to complete a 12-week course of oxacillin and 6-week course of rifampin. At week 12, the patient displayed clinical and radiologic evidence of cure.

4. Discussion

Vancomycin treatment failure has been defined by the presence of persistently positive blood or sterile site cultures after 7 or 21 days of treatment with vancomycin, respectively, and has been previously described in association with hVISA (Charles et al., 2004). Our case is unique in that, to our knowledge, it is the first report of a vancomycin treatment failure that occurred in association with the emergence of vancomycin heteroresistance in an MSSA isolate. The rapid sequence of increasing resistance separately highlights the capacity of *S. aureus* to evolve toward overt resistance in response to clinical vancomycin use.

Current evidence indicates that vancomycin heteroresistance in *S. aureus* represents an obligatory intermediate on the pathway to overt intermediate-level vancomycin resistance (Sieradzki et al., 1999). Previous studies have described the emergence of intermediate-type vancomycin resistance from vancomycin-heteroresistant MRSA (Bobin--Dubreux et al., 2001; Sieradzki et al., 1999). The isolates described here, however, offer a unique window into the critical “first steps” toward overt resistance in the absence of methicillin resistance. In addition, the proclivity of these strains to develop increased resistance in response to only 36 days of vancomycin may help further explain the recent increase in reported rates of vancomycin treatment failure (Sakoulas and Moellering, 2008). Awaiting further studies,

this case highlights the ability of hVISA isolates to evolve toward intermediate-type resistance in response to clinical use of vancomycin, and it emphasizes the lack of biologic association between methicillin and vancomycin resistance.

Acknowledgments

The authors thank the staff of the New York Hospital Clinical Microbiology Laboratory for their assistance and cooperation. This work was supported by grant AI 007613 from the National Institutes of Health.

References

- Bernard L, Vaudaux P, Rohner P, Huggler E, Armanet M, Pittet D, Lew DP, Schrenzel J. Comparative analysis and validation of different assays for glycopeptides susceptibility among methicillin-resistant *Staphylococcus aureus* strains. J Microbiol Methods. 2004; 57:231–239. [PubMed: 15063063]
- Bobin-Dubreux S, Reverdy M, Nervi C, Rougier M, Bolmström A, Vandenesch F, Etienne J. Clinical isolate of vancomycin-heterointermediate *Staphylococcus aureus* susceptible to methicillin and in vitro selection of a vancomycin-resistant derivative. Antimicrob Agents Chemother. 2001; 45:349–352. [PubMed: 11120996]
- Charles P, Ward P, Johnson P, Howden B, Grayson M. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clin Infect Dis. 2004; 38:448–451. [PubMed: 14727222]
- Fowler VG Jr, Miro JM, Hoen B, Cabell CH, Abrutyn E, Rubinstein E, Corey GR, Spelman D, Bradley SF, Barsic B, Pappas PA, Anstrom KJ, Wray D, Fortes CQ, Anguera I, Athan E, Jones P, van der Meer JT, Elliott TS, Levine DP, Bayer AS. ICE Investigators. *Staphylococcus aureus* endocarditis: a consequence of medical progress. JAMA. 2005; 293:3012–3021. [PubMed: 15972563]
- Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover F. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother. 1997; 40:135–136. [PubMed: 9249217]
- Mulver M, Chui L, Ismail J, Louie L, Murph C, Chang N, Alfa M. Canadian Committee for the Standardization of Molecular Methods. Development of a Canadian standardized protocol for subtyping methicillin-resistant *Staphylococcus aureus* using pulsed-field gel electrophoresis. J Clin Microbiol. 2001; 39:3481–3485. [PubMed: 11574559]
- Rossney A, Herra C, Brennan G, Morgan P, O'Connell B. Evaluation of the Xpert methicillin-resistant *Staphylococcus aureus* (MRSA) assay using the GeneXpert real-time PCR platform for rapid detection of MRSA from screening specimens. J Clin Microbiol. 2008; 46:3285–3290. [PubMed: 18685003]
- Rybak M, Leonard S, Rossi K, Cheung C, Sadar H, Jones R. Characterization of vancomycin-heteroresistant *Staphylococcus aureus* from the metropolitan area of Detroit, Michigan, over a 22-year period (from 1986 to 2007). J Clin Microbiol. 2008; 46:2950–2954. [PubMed: 18632899]
- Sakoulas G, Moellering R. Increasing antibiotic resistance among methicillin-resistant *Staphylococcus aureus* strains. Clin Infect Dis. 2008; 46:S360–S367. [PubMed: 18462091]
- Sieradzki K, Roberts R, Haber S, Tomasz A. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. N Engl J Med. 1999; 340:517–523. [PubMed: 10021472]
- Wootton M, MacGowan A, Walsh T, Howe R. A multicenter study for evaluating the current strategies for isolating *Staphylococcus aureus* strains with reduced susceptibility to glycopeptides. J Clin Microbiol. 2007; 45:329–332. [PubMed: 17108069]
- Yusof A, Engelhardt A, Karlson A, Bylund L, Vidh P, Mills K, Wootton M, Walsh TR. Evaluation of a new Etest vancomycin–teicoplanin strip for detection of glycopeptide-intermediate *Staphylococcus aureus* (GISA) in particular, heterogeneous GISA. J Clin Microbiol. 2008; 46:3042–3047. [PubMed: 18596146]

Fig. 1. Identification of isogenic *S. aureus* isolates demonstrating evolving heteroresistance to vancomycin from a patient with recurrent bacteremia and repeated courses of vancomycin. (A) Antibiotic susceptibility profiles of sequential isolates-note decreasing size of teicoplanin zone of inhibition and progressive increase in Etest, Macro Etest and PAP-AUC. (B) PFGE demonstrating clonality of all three isolates. (C) Clinical timeline of events

indicating sequence of isolates (day 11, day 15, day 47) in relation to hospitalization and vancomycin chemotherapy.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript