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Should the Currently Recommended Twice-Daily Dosing Still be Considered the Most Appropriate Regimen for Treating MRSA Ventilator-Associated Pneumonia with Vancomycin?

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Abstract

Meticillin-resistant (methicillin-resistant) *Staphylococcus aureus* causes unacceptably high mortality from ventilator-associated pneumonia, even when appropriate early therapy with vancomycin is administered at a dosage of 15 mg/kg every 12 hours. However, because of the poor penetration of vancomycin in epithelial lining fluid, it is unlikely that this dosing schedule always achieves optimal vancomycin exposure in the lung. Conversely, there is probably enough evidence to suggest that continuous infusion enhances vancomycin efficacy with the standard 30 mg/kg daily dosage, thus avoiding the need to use higher daily dosages that could increase the risk of nephrotoxicity. It is worth noting that in the case of fully susceptible pathogens with a minimum inhibitory concentration (MIC) of ≤1 mg/L, the strategy of targeting a steady-state vancomycin concentration of 15 mg/L during continuous infusion may simultaneously enable an area under the plasma concentration-time curve (AUC)/MIC ratio of ≥360, so that both pharmacodynamic efficacy targets may be optimized.

1. What Does 'Early Appropriate Antimicrobial Therapy' Mean when Treating Meticillin-Resistant *Staphylococcus aureus* (MRSA) Ventilator-Associated Pneumonia (VAP) with Vancomycin?

Meticillin-resistant (methicillin-resistant) *Staphylococcus aureus* (MRSA) is one of the most common and challenging bacteria causing ventilator-associated pneumonia (VAP), the most frequent infection occurring among intensive care unit (ICU) patients. The overall high attributable mortality rate for MRSA-VAP ranges between 25% and 56%;[1-3] thus, prompt and appropriate empirical antibacterial treatment is mandatory whenever this infection is suspected.

Vancomycin has been the drug of choice for MRSA-VAP for many years, thus it is currently considered the natural comparator in randomized clinical trials when assessing the efficacy of new anti-MRSA agents for the treatment of pneumonia.[2-4]

Although this drug is already 50 years old, there is still no definitive evidence on how to use it appropriately.

A statement in the recent American Thoracic Society (ATS) guidelines suggested that rapid achievement of plasma trough (or minimum) concentrations (C_{min}) of 15–20 mg/L should be considered the optimal goal for the treatment of MRSA-VAP with

vancomycin.[5] Indeed, we agree with the need for this value of C_{min}, but the daily dosing regimen that was proposed – namely, 15 mg/kg every 12 hours – seems inconsistent with the goal of achieving it in the majority of cases.

This opened a debate on the opportunity of considering alternative options for ensuring optimal treatment of MRSA-VAP with vancomycin. Whereas some authors believe that higher daily dosages could be helpful, at least in some cases,[6] others are confident that alternative dosing regimens with the standard daily dosages may be worthwhile.[7]

The intent of this article is to provide some evidence showing that continuous infusion might be a helpful tool in enhancing the probability of achieving optimal exposure with the standard 30 mg/kg daily dosage for the treatment of MRSA-VAP with vancomycin, thus avoiding the need to use higher daily dosages that could increase the risk of nephrotoxicity.

The first step in this direction is to better define what is meant by 'early appropriate antimicrobial therapy' for MRSA-VAP with vancomycin.

In the past 10 years, several major trials assessing the clinical outcome of VAP treatment in critically ill ICU patients have reported that initially inappropriate antibacterial therapy was significantly associated with higher mortality either generally or in specific population subsets.[8,9] However, in the specific context of staphylococcal VAP, it was recently reported that even when initially appropriate therapy with a glycopeptide was administered, MRSA-VAP may have been associated with either unacceptably high mortality[10] or prolongation of the ICU stay,[11] thus seeming to strengthen the hypothesis that glycopeptides may be suboptimal for treating MRSA-VAP.

We argue that these apparently negative findings might be at least partially explained by revisiting the concept of 'early appropriate antimicrobial therapy', which is currently based only on the spectrum of activity and the timing of administration. In fact, in the medical literature, the need for optimal drug exposure at the infection site for appropriate treatment of deep-seated infections is gaining increasing relevance.[12]

2. Towards an Optimization of Exposure with Vancomycin in the Treatment of MRSA VAP

Vancomycin exhibits time-dependent antibacterial activity, and the major efficacy determinant is considered the time during which the plasma concentration persists above the minimum inhibitory concentration (MIC) [T>MIC] of the aetiological agent. Accordingly, the goal of therapy should be early achievement and maintenance of plasma trough concentrations above the MIC (C_{min}>MIC), as this approach ensures optimal exposure for the entire dosing interval (T>MIC of 100%).[12] Consistently, in a recent case report, meticulous maintenance of plasma trough concentrations of >10 mg/L during vancomycin therapy was considered to be one of the most important factors for a successful clinical outcome and prevention of the spread of resistance, even in the case of long-term treatment.[13]

However, it might be argued that an assumption that the T>MIC is the only important parameter may lead to inappropriate dosing strategies,[14] since, in some studies, an area under the plasma concentration-time curve (AUC)/MIC ratio of 350–400, rather than the T>MIC, was found to be the best predictor of vancomycin efficacy.[15]

This may be an especially relevant issue when treating VAP, considering that vancomycin exhibits poor penetration in epithelial lining fluid, corresponding to about 5–25% of simultaneous plasma concentrations.[6,16]

Accordingly, we believe that an alternative dosing regimen allowing simultaneous achievement of both a steady-state concentration (C_{ss}) of 15 mg/L and an AUC/MIC ratio of ≥360 could be the optimal choice for MRSA-VAP therapy with vancomycin.

Of note, in a recent retrospective study assessing trough plasma concentrations 36–48 hours after starting vancomycin therapy with standard dosages according to nomograms, among the 780 patients receiving the drug in 2–4 separate daily doses, the observed C_{min} values were <10 mg/L in 45.1% of cases and even <5 mg/L in a remarkable 19% of cases.[17]

Importantly, even greater underexposure may be expected in patients with pathophysiological conditions that increase the volume of the extracellular space (e.g. polytrauma or fluid overload) or that enhance renal clearance of hydrophilic antimicrobials (e.g. hyperdynamic sepsis, extensive burns or leukaemia).[18] In a study carried out in febrile neutropenic patients with acute leukaemia empirically treated with vancomycin at a mean daily dosage of 15 mg/kg every 12 hours, we found that on day 3, the C_{min} averaged 5.23 mg/L and was <5 mg/L in as many as 56% of cases.[19]

Overall, these data indicate that the standard twice-daily regimen of vancomycin may frequently cause suboptimal drug exposure in critically ill patients, and thus support the need for a more aggressive dosing regimen for appropriate treatment of MRSA pneumonia.

3. Continuous Infusion: A Potentially Useful Tool for Improving the Efficacy of the Fixed 30 mg/kg Daily Vancomycin Dosage

Conversely, continuous infusion may be a powerful tool for enhancing the clinical efficacy of vancomycin with the fixed 30 mg/kg daily dosage, thus avoiding the need to use higher daily dosages that might potentially increase the nephrotoxicity risk.[7] In fact, with the total daily dosage being the same, this approach may ensure higher and more sustained plasma steady-state trough concentrations than intermittent dosing (figure 1), without causing higher total daily drug exposure in terms of the AUC from 0 to 24 hours (AUC_{24} being equal to $dose_{24h}$/clearance).

Interestingly, it should be noted that targeting the steady-state vancomycin concentration during continuous infusion at 15 mg/L may simultaneously enable an AUC/MIC ratio of ≥360 against susceptible pathogens with an MIC of ≤1 mg/L.[20] Although in some countries, vancomycin MICs for MRSA isolates are currently shifting towards higher values,[21] this approach may still optimize exposure with vancomycin against fully susceptible MRSA strains with an MIC of ≤1 mg/L.

On the basis of this rationale, since 2001 the University of Udine teaching hospital (Udine, Italy) has treated proven or suspected MRSA infections in critically ill patients by administering the standard vancomycin dosage of 30 mg/kg/day as a continuous infusion. This regimen has subsequently been refined by the use of nomograms to adjust the infusion according to the patient's renal function. In most cases, this has achieved correct pharmacokinetic exposure (in terms of rapid achievement and maintenance of a plasma concentration of 15 mg/L) and a favourable clinical outcome with no evidence of nephrotoxicity (personal unpublished data). When choosing a continuous vancomycin infusion, it must be remembered that to rapidly achieve therapeutically effective concentrations, an initial loading dose of 15 mg/kg (corresponding to the first dose of intermittent dosing) must always be administered, irrespective of the patient's renal function, with the continuous infusion starting immediately afterwards. This approach may, in fact, enable rapid achievement of therapeutically effective concentrations, thus avoiding the risk of underexposure, which may occur in the first hours of treatment when applying only a continuous infusion.

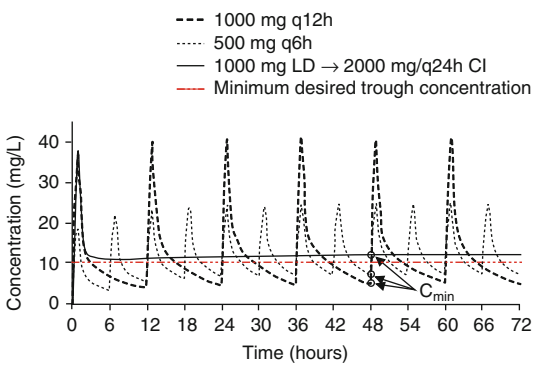

Fig. 1. Simulated profiles of daily vancomycin plasma exposure achievable in a young male with normal renal function (age 40 y, bodyweight 67 kg, height 170 cm, serum creatinine 0.6 mg/dL, estimated creatinine clearance 2.31 mL/min/kg) when administering the fixed 30 mg/kg daily dosage separated into two or four intermittent infusions, or by continuous infusion (CI) after a loading dose (LD). The simulation was performed using a two-compartment linear model by means of the Abbottbase Pharmacokinetic Systems program (version 1.10) from Abbott Laboratories Diagnostics Division. **C_{min}** = minimum plasma concentration; **q*x*h** = every *x* hours.

According to these theoretical considerations, in the aforementioned retrospective analysis of vancomycin therapeutic drug monitoring (TDM), the initial C_{min} was suboptimal in only a minority of the 957 patients receiving vancomycin by continuous infusion, being <10 mg/L in 7.9% of cases and <5 mg/L in only 1.6% of cases.[17]

4. Is There Any Evidence of the Clinical Usefulness of Continuous Infusion with Vancomycin?

As far as efficacy is concerned, it may be argued that in the only large, prospective, randomized, multicentre study comparing continuous and intermittent infusion of vancomycin, no definitive advantage of the former was observed, although comparable efficacy and tolerability of the two dosing schedules was documented.[22]

However, in a recent retrospective study carried out in patients treated with vancomycin for oxacillin-resistant VAP, Rello et al.[10] showed that continuous infusion of vancomycin was independently associated with lower mortality than intermittent infusion (25% vs 54.2%, p = 0.02). Indeed, this was the first clinical study supporting the potential usefulness of continuous infusion in enhancing the clinical efficacy of vancomycin, although caution was expressed because of the retrospective nature of the study and the small number of patients receiving such a regimen (n = 16).[23]

Additionally, in an *in vitro* experience assessing the bactericidal activity of vancomycin in serum from healthy volunteers receiving vancomycin as a continuous or intermittent infusion, it was suggested that a continuous infusion may be helpful in increasing efficacy, especially against isolates with reduced susceptibility to vancomycin.[24]

Overall, these findings seem to support the hypothesis that continuous infusion may be a useful tool to optimize vancomycin pharmacodynamics in the treatment of deep-seated infections,

especially in the presence of borderline-susceptible pathogens, as may frequently occur in late-onset VAP. For these reasons, we call for more intensive studies of this approach.

5. Is Optimized Vancomycin Pharmacokinetic/Pharmacodynamic Exposure Correlated with Clinical Outcome? Point and Counterpoint

While awaiting the results of prospective trials to definitely clarify the role of continuous infusion, it is interesting to note that the relationship between antimicrobial exposure and the clinical outcome in patients with MRSA pneumonia treated by intermittent dosing with vancomycin was assessed in two interesting studies published in October 2006; however, conflicting results were reported.

The first study[25] was a retrospective analysis carried out in adult patients with healthcare-associated pneumonia due to MRSA who required hospitalization and received initial vancomycin therapy at 30 mg/kg divided into two daily doses, starting within 12 hours of the isolation of MRSA from bronchoalveolar lavage. Briefly, among the 102 evaluable patients, the mean vancomycin exposure in survivors (n = 70) was not significantly different from that in nonsurvivors (n = 32) in terms of either trough concentrations (C_{min} 13.6 ± 5.9 vs 13.9 ± 6.7 mg/L, p = 0.86) or total daily exposure (AUC 351 ± 143 vs 354 ± 109 mg • h/L, p = 0.94). However, among patients with a C_{min} of ≥15 mg/L, an interesting trend towards a greater proportion of fever resolution after 72 hours of treatment was observed (87.5% vs 69.7%, p = 0.055). On the other hand, among nonsurvivors, the mortality rate was similar – irrespective of stratification for drug exposure – in terms of the C_{min} (about 25–35% for any level of the C_{min} <10, 10–15, 15–20 or >20 mg/L) and the AUC (about 30–40% for any level of the AUC <200, 201–300, 301–400, >400 mg • h/L), suggesting no clear relationship between drug exposure and the clinical outcome. Accordingly, the investigators questioned the recommendation to achieve vancomycin steady-state trough concentrations of ≥15 mg/L as a predictor of a successful patient outcome. These surprising findings, although potentially indicating the poor usefulness of clinical pharmacodynamics in predicting the clinical efficacy of antimicrobials, must be interpreted with extreme caution owing to some major drawbacks of the study, as partially recognised by the investigators. First, it was a retrospective analysis, conducted over a 6.5-year period between 1999 and 2005, among patients receiving an initial vancomycin dosing regimen of 15 mg/kg every 12 hours, which, as previously discussed, is probably a suboptimal schedule for rapid achievement of trough concentrations of 15 mg/L. Second, the MICs of the isolates were not directly measured but were estimated by measuring the disk zone diameter of the Kirby-Bauer test. Most importantly, the time to achievement of a vancomycin steady-state trough concentration of 15 mg/L as a predictor of the outcome was not assessed, and the timing of TDM from the beginning of therapy was not specified. Additionally, drug exposure (namely, the AUC) was not directly measured but simply estimated, and 14 patients did not have a measured vancomycin trough concentration. These limits pose some doubts about the validity of the conclusions drawn and raise concerns about their generalizability.

Conversely, from a methodological point of view, the second study[26] may be considered a valid example of how clinical pharmacodynamic studies may be helpful in assessing the clinical efficacy of antimicrobials. It was a prospective cohort study of adult patients infected with nosocomial MRSA (most with pneumonia), in which the medical and laboratory records of eligible patients were retrospectively reviewed with the aim of determining the distribution of vancomycin MICs (a low MIC was defined as ≤1 mg/L, n = 51; a high MIC was defined as 1.5 or 2 mg/L, n = 44) of MRSA clinical isolates and treatment outcomes with vancomycin dosages targeting an unbound trough concentration of at least four times the MIC (i.e. the theoretically maximized pharmacodynamic exposure for time-dependent antimicrobials). Interestingly, considering the 95 evaluable patients, in those who promptly achieved the optimal target trough concentration, a significantly higher overall initial response rate was observed within the first 72 hours (76% vs 56%, p = 0.05), irrespective of the pattern of susceptibility of MRSA isolates. When assessing the final response outcome, the relevance of drug exposure in relation to MRSA susceptibility became even more evident: a significantly higher favourable response rate in patients achieving optimal exposure was documented only if the MRSA isolate had a low MIC (85% vs 62% for low vs high MIC MRSA isolates; p = 0.02). On the basis of these findings and in agreement with the ATS guidelines, the investigators suggested aggressive initial dosing to achieve a vancomycin trough concentration of 15 mg/L or more. However, when assessing treatment safety, a high vancomycin trough concentration (highest value 27.5 ± 8.3 vs 19.1 ± 6.4 mg/L, p < 0.001) was found to be one of the two most relevant variables probably associated with nephrotoxicity. These data suggest that pursuit of a C_{min} of 15 mg/L with intermittent dosing may cause excessive drug exposure and thus an increased nephrotoxicity risk. Finally, for invasive infections caused by MRSA strains with an MIC of 2 mg/L, alternative treatment options (namely, linezolid) were advocated.

6. Conclusions

Overall, the arguments discussed in this clinical commentary and the analysis of these two articles offer the opportunity for some relevant remarks.

First, it is extremely important that, from the start of treatment, appropriate pharmacodynamic exposure is achieved rapidly at the infection site with the correct antimicrobial agent, since an inappropriate dosing regimen may potentially hamper the clinical outcome. In this perspective, for empirical antistaphylococcal therapy with vancomycin, timely loading at 15 mg/kg over 2 hours followed by continuous infusion of 30 mg/kg/day would probably ensure appropriate pharmacodynamic exposure in most cases.

Second, considering the increased nephrotoxicity risk observed in patients with very high trough concentrations when using high intermittent dosing,[26] continuous infusion may be effective in enhancing the efficacy of vancomycin while avoiding the potentially increased nephrotoxicity risk related to the need for higher daily dosages. In fact, this approach may significantly increase trough concentrations to values approaching 15 mg/L without increasing the total daily drug exposure, since the total daily dosage (30 mg/kg) is the same as with intermittent dosing.

Finally, the suggestion by Hidayat et al.[26] to use alternative treatment in the presence of MRSA with a high MIC for vancomycin (1.5–2 mg/L) is in line with our previously proposed algorithm for empirical treatment of MRSA-VAP.[12] In this algorithm, vancomycin (always administered by continuous infusion) is suggested when fully susceptible pathogens are involved (MIC ≤0.5 mg/L) and, given the wide interindividual pharmacokinetic variability frequently observed in critically ill patients, tailoring of drug exposure by means of TDM 48–72 hours after starting therapy is recommended. Conversely, against MRSA strains with MIC values for vancomycin of ≥1 mg/L – considering that, despite theoretical *in vitro* susceptibility, these concentrations may be very difficult to achieve consistently in epithelial lining fluid with vancomycin with the current recommendations – we use linezolid as alternative choice, in agreement with the ATS guidelines.[5] Interestingly, a recent survey showed that the switch to newer antimicrobial agents was the treatment approach most frequently used by infectious diseases consultants treating patients with persistent bacteraemia due to MRSA with vancomycin MICs approaching the limit of susceptibility.[27]

We believe that these pharmacodynamic concepts are extremely important, since a correct definition of appropriate vancomycin use may be relevant not only in improving its efficacy in daily clinical practice, but also in planning comparative clinical trials of new antimicrobial agents. Currently, the renaissance of research interest in antimicrobial chemotherapy is leading to a significant improvement in the therapeutic armamentarium of anti-MRSA agents; therefore, it becomes mandatory that efficacy data on the new antimicrobials come from studies where the correct comparator – administered with the best dosing schedule according to pharmacodynamic principles – is chosen.

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References

1. Gonzalez C, Rubio M, Romero-Vivas J, et al. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis 1999; 29: 1171-7
2. Wunderink RG, Rello J, Cammarata SK, et al. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. Chest 2003; 124: 1789-97
3. Fagon J, Patrick H, Haas DW, et al. Treatment of gram-positive nosocomial pneumonia: prospective randomized comparison of quinupristin/dalfopristin versus vancomycin. Nosocomial Pneumonia Group. Am J Respir Crit Care Med 2000; 161: 753-62
4. Rubinstein E, Cammarata S, Oliphant T, et al. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 2001; 32: 402-12
5. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416
6. Scheetz MH, Wunderink RG, Postelnick MJ, et al. Potential impact of vancomycin pulmonary distribution on treatment outcomes in patients with methicillin-resistant *Staphylococcus aureus* pneumonia. Pharmacotherapy 2006; 26: 539-50
7. Viale P, Pea F. What does it mean: appropriate therapy for methicillin-resistant *Staphylococcus aureus*? [letter]. Crit Care Med 2007; 35: 991
8. Clec'h C, Timsit JF, De Lassence A, et al. Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: influence of disease severity. Intensive Care Med 2004; 30: 1327-33
9. Niederman MS. Use of broad-spectrum antimicrobials for the treatment of pneumonia in seriously ill patients: maximizing clinical outcomes and minimizing selection of resistant organisms. Clin Infect Dis 2006; 42 Suppl. 2: S72-81
10. Rello J, Sole-Violan J, Sa-Borges M, et al. Pneumonia caused by oxacillin-resistant *Staphylococcus aureus* treated with glycopeptides. Crit Care Med 2005; 33: 1983-7
11. Shorr AF, Combes A, Kollef MH, et al. Methicillin-resistant *Staphylococcus aureus* prolongs intensive care unit stay in ventilator-associated pneumonia, despite initially appropriate antibiotic therapy. Crit Care Med 2006; 34: 700-6
12. Pea F, Viale P. The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? Clin Infect Dis 2006; 42: 1764-71

13. Sakoulas G, Gold HS, Cohen RA, et al. Effects of prolonged vancomycin administration on methicillin-resistant *Staphylococcus aureus* (MRSA) in a patient with recurrent bacteraemia. J Antimicrob Chemother 2006; 57: 699-704
14. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 2006; 42 Suppl. 1: S35-9
15. Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet 2004; 43: 925-42
16. Lamer C, de Beco V, Soler P, et al. Analysis of vancomycin entry into pulmonary lining fluid by bronchoalveolar lavage in critically ill patients. Antimicrob Agents Chemother 1993; 37: 281-6
17. Kitzis MD, Goldstein FW. Monitoring of vancomycin serum levels for the treatment of staphylococcal infections. Clin Microbiol Infect 2006; 12: 92-5
18. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 2005; 44: 1009-34
19. Pea F, Poz D, Baraldo M, et al. Optimisation of vancomycin regimen in neutropenic haematological patients with normal renal function: multiple daily doses may be preferable. Clin Drug Invest 2000; 19: 213-8
20. Pea F, Viale P. Pharmacodynamics of antibiotics to treat multidrug-resistant Gram-positive hospital infections. Expert Rev Anti Infect Ther 2007; 5: 255-70
21. Wang G, Hindler JF, Ward KW, et al. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol 2006; 44: 3883-6
22. Wysocki M, Delatour F, Faurisson F, et al. Continuous versus intermittent infusion of vancomycin in severe staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother 2001; 45: 2460-7
23. Blot S. MRSA pneumonia: better outcome through continuous infusion of vancomycin? Crit Care Med 2005; 33: 2127-8
24. Klepser ME, Patel KB, Nicolau DP, et al. Comparison of bactericidal activities of intermittent and continuous infusion dosing of vancomycin against methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecalis*. Pharmacotherapy 1998; 18: 1069-74
25. Jeffres MN, Isakow W, Doherty JA, et al. Predictors of mortality for methicillin-resistant *Staphylococcus aureus* health-care-associated pneumonia: specific evaluation of vancomycin pharmacokinetic indices. Chest 2006; 130: 947-55
26. Hidayat LK, Hsu DI, Quist R, et al. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med 2006; 166: 2138-44
27. Hageman JC, Liedtke LA, Sunenshine RH, et al. Management of persistent bacteremia caused by methicillin-resistant *Staphylococcus aureus*: a survey of infectious diseases consultants. Clin Infect Dis 2006; 43: e42-5

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