

NOTES

Impact of Empirical-Therapy Selection on Outcomes of Intravenous Drug Users with Infective Endocarditis Caused by Methicillin-Susceptible *Staphylococcus aureus*[▽]Thomas P. Lodise, Jr.,^{1*} Peggy S. McKinnon,² Donald P. Levine,^{3,4} and Michael J. Rybak^{3,4,5}*Albany College of Pharmacy, Albany, New York*¹; *Barnes-Jewish Hospital, St. Louis, Missouri*²; *School of Medicine, Wayne State University, Detroit, Michigan*³; *Detroit Receiving Hospital and University Health Center, Detroit, Michigan*⁴; and *Anti-Infective Laboratory, College of Pharmacy & Health Sciences, Wayne State University, Detroit, Michigan*⁵

Received 24 January 2007/Returned for modification 15 March 2007/Accepted 23 July 2007

This study compares beta-lactam and vancomycin among intravenous drug users with infective endocarditis caused by methicillin-susceptible *Staphylococcus aureus*. Patients who received vancomycin had higher infection-related mortality, even if they were switched to beta-lactam once culture results became available; this relationship persisted after logistic regression analysis controlling for clinical characteristics.

Many clinicians believe that vancomycin is inferior to beta-lactam antibiotics for the treatment of serious methicillin-susceptible *Staphylococcus aureus* (MSSA) infections. This notion is largely based on in vitro data demonstrating that vancomycin does not kill MSSA as effectively as a beta-lactam (2, 18). Although the results have been consistent, there are limited clinical data to support this belief (1, 3, 4, 5, 6, 8, 11, 17, 18). While infective endocarditis (IE) caused by *S. aureus* (MSSA IE) occurs frequently in injection drug users (IDUs), treatment outcome data for MSSA IE are sparse and have been limited primarily to comparisons among IDUs with right-sided MSSA IE of small sample sizes (3, 5, 7, 14, 16, 18). Thus, this investigation provides additional insights as to whether empirical beta-lactam therapy is superior to empirical vancomycin therapy for this vulnerable population. (This study was presented in part at the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, September 2002.)

Setting. The study was conducted at Detroit Receiving Hospital, a 279-bed urban level I trauma center.

Study population. The study included all confirmed hospitalized patients with IE caused by *S. aureus* among IDUs treated between 1 January 1997 and 31 July 2001. The study included only those patients who met the following criteria: (i) positive MSSA bloodstream infection, (ii) MSSA bloodstream infection satisfying the modified Duke criteria for IE (13), (iii) documented recent use of intravenous drugs prior to admission in the medical record, and (iv) empirical treatment with vancomycin or a beta-lactam. This study was approved by the Wayne State University Human Investigation Committee.

Study design. A retrospective population-based cohort analysis was performed. Data extracted from the medical record

included age, sex, admitting service, classification by Duke criteria status, the valve involved, microbiological data, human immunodeficiency virus (HIV) infection status, antibiotic treatment, metastatic embolic complications (e.g., pulmonary emboli and splenic emboli, etc.) present at diagnosis, performance of surgery, and outcome.

Microbiology. Microbiological data included all positive *S. aureus* cultures. Results of susceptibility testing were performed, interpreted, and recorded according to NCCLS guidelines (15).

Treatment data. All antimicrobials administered were noted. Empirical therapy was defined as the antibiotic administered prior to the identification and determination of the susceptibility of the infecting organism (10). Empirical antibiotic therapy was classified as either a vancomycin regimen or a beta-lactam-containing regimen. Patients who received both beta-lactam and vancomycin were classified in the beta-lactam-containing group. Definitive therapy was classified as the antibiotic regimen administered after the identification and determination of the antibiotic susceptibility of the infecting organism. During the study, vancomycin was dosed by a nomogram that targeted troughs of between 12 and 15 mg/liter, as described elsewhere (9). As vancomycin levels are not routinely monitored at our institution, vancomycin trough levels were available for only five patients, and the median (range) vancomycin trough was 18.6 mg/liter (14.5 to 29.0).

Outcome assessment. The following outcome was assessed: death related to MSSA IE (infection-related mortality). Death was attributed to MSSA IE (infection-related mortality) when at least one of the following indications was present: (i) blood cultures were positive for MSSA at the time of death; (ii) death occurred before the resolution of IE symptoms; (iii) death occurred during hospitalization without an unrelated, alternative cause; and (iv) autopsy found *S. aureus* infection as a cause of death (13).

* Corresponding author. Mailing address: Albany College of Pharmacy, 106 New Scotland Avenue, Albany, NY 12208-3492. Phone: (518) 445-7292. Fax: (518) 445-7302. E-mail: lodiset@acp.edu.

[▽] Published ahead of print on 30 July 2007.

TABLE 1. Comparison of baseline clinical characteristics and outcomes for patients with MSSA IE who received empirical beta-lactam therapy and for those who received empirical vancomycin therapy

Baseline clinical feature or overall outcome	Result for ^a :		P value
	Beta-lactam (n = 44)	Vancomycin (n = 28)	
Baseline clinical features			
Mean age (SD) (yr)	42.6 (6.3)	40.7 (8.3)	0.5
Sex (males)	26 (59.1)	13 (46.4)	0.3
HIV infection	11 (25.0)	3 (10.7)	0.1
AIDS	4 (9.1)	2 (7.1)	0.8
Status according to Duke criteria			
Definite IE	36 (81.8)	27 (96.4)	0.07
Possible IE	8 (18.2)	1 (11.1)	
Heart side involvement			
Left side/bilateral	11 (25.0)	9 (32.1)	0.5
Right side	33 (75.0)	19 (67.9)	
Native valve	44 (100.0)	29 (100.0)	
Metastatic embolic complications present at diagnosis	31 (72.1)	23 (79.3)	0.5
Concomitant aminoglycoside usage	32 (72.7)	21 (75.0)	0.8
Pulse (once-daily) daily dosing ^b	14 (31.8)	12 (42.9)	0.5
Intermittent (traditional) daily dosing ^c	17 (38.6)	9 (32.1)	0.5
Concomitant rifampin usage	1 (2.3)	2 (7.1)	0.3
Surgical intervention	1 (2.3)	1 (3.6)	0.7
Overall outcome (infection-related mortality) for indicated patient group			
All	5 (11.4)	11 (39.3)	0.005
Left-side/bilateral involvement	3 (27.3)	6 (66.7)	0.08
Right-side involvement	2 (6.1)	5 (26.3)	0.04
Definite IE by Duke criteria (%)	5 (13.9)	11 (40.7)	0.02

^a Except for the mean age data, all data are presented as numbers of patients (with percentages respective to the total number in the indicated therapy group in parentheses).

^b Dose: 3 mg/kg of body weight/day as one daily dose.

^c Dose: 3 mg/kg of body weight/day in three divided doses.

Statistical analysis. Bivariate associations between empirical treatment selection and outcome were assessed using Pearson χ^2 or Fisher's exact test (categorical variables) and Student's *t* or the Mann-Whitney U test (continuous variables). Logistic regression was used to estimate the independent association of empirical treatment selection with infection-related mortality while adjusting for baseline clinical characteristics. All calculations were performed with SPSS software, version 10.0 (SPSS, Chicago, IL).

During the 5-year study period, there were 98 episodes of IE caused by *S. aureus* among IDUs. Of the 84 MSSA cases, 72 received either vancomycin (*n* = 28) or beta-lactam (*n* = 44). Of the 44 beta-lactam patients, 36 received semisynthetic penicillin and 8 received ceftriaxone. Twelve additional patients were enrolled in an investigational antibiotic study and are excluded from this analysis. Of the 72 patients, 16 died, and all cases of mortality were considered infection related.

Bivariate comparison of baseline clinical features for 72 MSSA patients between treatment groups detected no statistical differences (Table 1). The groups were similar with respect to age, sex, HIV infection status, the valve involved, the presence of metastatic embolic complications at diagnosis, concomitant aminoglycoside usage, once-daily versus traditional aminoglycoside dosing, concomitant usage of rifampin, and performance of surgical intervention. The median duration of concomitant aminoglycoside usage was longer for beta-lactam patients than for vancomycin patients (5.5 days versus 3.0 days; *P* = 0.07). Compared to vancomycin patients, those receiving beta-lactams were more often HIV positive (10.7%

and 25.0%, respectively; *P* = 0.1) and less likely to have definite IE (96.4% and 81.8%, respectively; *P* = 0.07).

The outcome analysis detected significantly high infection-related mortality in the vancomycin group compared to that for the beta-lactam group (39.4% versus 11.4%; *P* = 0.005) (Table 1). Among beta-lactam patients, the infection-related mortality rate was higher for patients that received ceftriaxone than for the semisynthetic penicillin patients, but the difference was not significant (25.0% versus 8.3%; *P* = 0.2). Vancomycin use remained highly predictive of infection-related mortality after logistic regression analysis adjusted for age, sex, HIV infection status, Duke criteria status, the valve involved, the presence of metastatic embolic complications at diagnosis, concomitant aminoglycoside usage, and the duration of aminoglycoside use (adjusted odds ratio, 6.5; 95% confidence interval, 1.4 to 29.4). Among patients with left-side/bilateral involvement, infection-related mortality was higher among vancomycin patients than among beta-lactam patients (66.7% versus 27.3%) but the difference was not significant (*P* = 0.08). For patients with right-sided disease only, infection-related mortality was significantly higher among vancomycin patients (26.3% versus 6.1%; *P* = 0.04). Among patients with definite IE, infection-related mortality was significantly higher among vancomycin patients (40.7% versus 13.9%; *P* = 0.02). Of the 28 patients who were started on vancomycin, 22 had vancomycin changed to an alternative primary regimen, 21 were changed to a semisynthetic penicillin, and 1 was switched to quinupristin-dalfopristin. Patients received vancomycin for a median of 3 days (interquartile range, 3 to 4 days) prior to being switched. No difference

between infection-related mortalities was noted for patients who received vancomycin as the primary regimen and patients who had vancomycin switched to beta-lactam therapy (33.3% versus 40.9%; $P = 0.7$).

The results indicate that there are indeed differences in outcomes for IDUs with MSSA IE who received empirical beta-lactam therapy and for those who received vancomycin. Vancomycin patients had higher infection-related mortality by bivariate analysis, and this relationship persisted in the logistic regression analysis after controlling for baseline clinical characteristics. These findings support the notion that vancomycin is inferior to beta-lactam for the treatment of IDUs with MSSA IE. In addition, vancomycin patients switched to beta-lactam therapy once susceptibility results became available still had an infection-related mortality rate higher than that seen for patients treated with beta-lactam from the initiation of therapy. Based on these results, our institution advocates the inclusion of a beta-lactam in the empirical therapy for serious staphylococcal infection.

Several caveats should be noted when interpreting these results. First, this single-center analysis focused solely on IDUs with MSSA IE; the results may not be generalizable to other populations. Second, while the optimal way to compare antibiotic dosing regimens is through a randomized clinical trial, such a study would be difficult to execute for a variety of ethical and clinical reasons. Although this was a single-center retrospective cohort study, the two treatment groups were well balanced at baseline, and logistic regression was used to adjust for any lingering differences that may have introduced bias. Although the groups were well matched at baseline, the potential for selection bias still exists because of the observational nature of the study. For example, baseline serum creatinine levels, echocardiographic data, and estimated ejection fractions were not available and thus were not compared between treatment groups. Third, only two patients had a surgical intervention, and this may have impacted mortality, particularly in the left-sided disease group. Finally, the study outcomes were limited to objective endpoints due to the difficulty of assessing clinical response in the retrospective study design.

In conclusion, this study compared infection-related mortalities for empirical beta-lactam therapy and for vancomycin therapy among IDUs with MSSA IE. The results support the findings of other clinical series in suggesting that vancomycin is inferior to beta-lactam therapy for MSSA and confirms this for IDUs with MSSA IE. The results also suggest that the empirical therapy window is critical to outcomes, since vancomycin patients switched to beta-lactam therapy once susceptibility results became available still had outcomes inferior to those for patients treated with a beta-lactam from the initiation of therapy. Based on the observed results, empirical therapy with both a beta-lactam and an anti-methicillin-resistant *S. aureus* agent should be considered for serious *S. aureus* infections, and fur-

ther study of this novel combination empirical regimen in a randomized, prospective fashion is warranted.

The manuscript benefited greatly from the thoughtful editing of Allison Krug.

REFERENCES

1. **Bodi, M., C. Ardanuy, and J. Rello.** 2001. Impact of gram-positive resistance on outcome of nosocomial pneumonia. *Crit. Care Med.* **29**:N82–N86.
2. **Cantoni, L., M. P. Glauser, and J. Bille.** 1990. Comparative efficacy of daptomycin, vancomycin, and cloxacillin for the treatment of *Staphylococcus aureus* endocarditis in rats and role of test conditions in this determination. *Antimicrob. Agents Chemother.* **34**:2348–2353.
3. **Chambers, H. F., R. T. Miller, and M. D. Newman.** 1988. Right-sided Staphylococcus aureus endocarditis in intravenous drug abusers: two-week combination therapy. *Ann. Intern. Med.* **109**:619–624.
4. **Chang, F. Y., J. E. Peacock, Jr., D. M. Musher, P. Triplett, B. B. MacDonald, J. M. Mylotte, A. O'Donnell, M. M. Wagener, and V. L. Yu.** 2003. Staphylococcus aureus bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine (Baltimore)* **82**:333–339.
5. **Fortun, J., E. Navas, J. Martinez-Beltran, J. Perez-Molina, P. Martin-Davila, A. Guerrero, and S. Moreno.** 2001. Short-course therapy for right-side endocarditis due to Staphylococcus aureus in drug abusers: cloxacillin versus glycopeptides in combination with gentamicin. *Clin. Infect. Dis.* **33**:120–125.
6. **Fowler, V. G., Jr., L. K. Kong, G. R. Corey, G. S. Gottlieb, R. S. McClelland, D. J. Sexton, D. Gesty-Palmer, and L. J. Harrell.** 1999. Recurrent Staphylococcus aureus bacteremia: pulsed-field gel electrophoresis findings in 29 patients. *J. Infect. Dis.* **179**:1157–1161.
7. **Fowler, V. G., Jr., J. M. Miro, B. Hoen, C. H. Cabell, E. Abrutyn, E. Rubinstein, G. R. Corey, D. Spelman, S. F. Bradley, B. Barsic, P. A. Pappas, K. J. Anstrom, D. Wray, C. Q. Fortes, I. Anguera, E. Athan, P. Jones, J. T. van der Meer, T. S. Elliott, D. P. Levine, and A. S. Bayer.** 2005. Staphylococcus aureus endocarditis: a consequence of medical progress. *JAMA* **293**:3012–3021.
8. **Gonzalez, C., M. Rubio, J. Romero-Vivas, M. Gonzalez, and J. J. Picazo.** 1999. Bacteremic pneumonia due to Staphylococcus aureus: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. *Clin. Infect. Dis.* **29**:1171–1177.
9. **Karam, C. M., P. S. McKinnon, M. M. Neuhauser, and M. J. Rybak.** 1999. Outcome assessment of minimizing vancomycin monitoring and dosing adjustments. *Pharmacotherapy* **19**:257–266.
10. **Kollef, M. H., G. Sherman, S. Ward, and V. J. Fraser.** 1999. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* **115**:462–474.
11. **Levine, D. P., B. S. Fromm, and B. R. Reddy.** 1991. Slow response to vancomycin or vancomycin plus rifampin in methicillin-resistant Staphylococcus aureus endocarditis. *Ann. Intern. Med.* **115**:674–680.
12. **Li, J. S., D. J. Sexton, N. Mick, R. Nettles, V. G. Fowler, Jr., T. Ryan, T. Bashore, and G. R. Corey.** 2000. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin. Infect. Dis.* **30**:633–638.
13. **Lodise, T. P., P. S. McKinnon, L. Swiderski, and M. J. Rybak.** 2003. Outcomes analysis of delayed antibiotic treatment for hospital-acquired Staphylococcus aureus bacteremia. *Clin. Infect. Dis.* **36**:1418–1423.
14. **Mathew, J., T. Addai, A. Anand, A. Morrobel, P. Maheshwari, and S. Freels.** 1995. Clinical features, site of involvement, bacteriologic findings, and outcome of infective endocarditis in intravenous drug users. *Arch. Intern. Med.* **155**:1641–1648.
15. **NCCLS.** 2000. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. NCCLS document M2-A7. NCCLS, Wayne, PA.
16. **Reisberg, B. E.** 1979. Infective endocarditis in the narcotic addict. *Prog. Cardiovasc. Dis.* **22**:193–204.
17. **Rello, J., A. Torres, M. Ricart, J. Valles, J. Gonzalez, A. Artigas, and R. Rodriguez-Roisin.** 1994. Ventilator-associated pneumonia by Staphylococcus aureus. Comparison of methicillin-resistant and methicillin-sensitive episodes. *Am. J. Respir. Crit. Care Med.* **150**:1545–1549.
18. **Small, P. M., and H. F. Chambers.** 1990. Vancomycin for *Staphylococcus aureus* endocarditis in intravenous drug users. *Antimicrob. Agents Chemother.* **34**:1227–1231.