Journal of the American College of Cardiology
Vol. 51, No. 18, 2008

ISSN 0735-1097/08/$34.00

CORRESPONDENCE

Research Correspondence

Thrombocytopenia and Mortality in Infective Endocarditis

To the Editor: Infective endocarditis remains a life-threatening disease. Platelets have an important role in the pathogenesis of endocarditis (1) and are sensitive monitors of the systemic host response to sepsis. We have investigated the platelet response in infective endocarditis and its relationship to 6-month mortality.

We retrospectively reviewed consecutive cases of infective endocarditis admitted to Royal Prince Alfred Hospital (Sydney, Australia) between 1996 and 2006 and identified 192 patients meeting the modified Duke criteria for definite or possible endocarditis. Clinical and laboratory variables including those previously associated with adverse outcomes (2,3) were systematically collected at presentation to the emergency department (day 1), and at days 4, 8, and 12. Days 1 and 8 were pre-specified for detailed analysis because average platelet survival is 8 days, and previous studies have indicated that patient re-evaluation during treatment and consideration for surgery are typically performed after 1 week (2).

The primary outcome of all-cause mortality at 6 months after presentation was determined from medical records and the New South Wales Registry of Births, Deaths, and Marriages and was complete for 96.7% of patients. Patients with incomplete outcome data were censored according to their status at the time of last contact. Statistical comparisons were made using independent samples *t* test, chi-square test, and Cox proportional hazards regression models as indicated.

The clinical characteristics and outcomes of the cohort are summarized (Online Table 1). The patients were young and predominantly male. Left-sided infections were implicated in 78% of patients and prosthetic valve infections in 19% of patients. Blood cultures were positive in 83% of patients and *Staphylococcus aureus* was the most common organism isolated. Cardiac surgery was performed during the index admission in 30% of patients. The all-cause 6-month mortality was 24%.

Platelet counts were significantly lower among nonsurvivors than survivors at presentation ($138.3 \pm 86.8 \times 10^3/\mu l$ vs. $196.3 \pm 115.6 \times 10^3/\mu l$; $p < 0.01$), day 8 ($177.2 \pm 105.5 \times 10^3/\mu l$ vs. $327.9 \pm 141.7 \times 10^3/\mu l$; $p < 0.01$) and throughout the first 12 days of admission (Online Fig. 1). The severity of thrombocytopenia predicted 6-month mortality (Fig. 1). Exclusion of patients with pre-morbid thrombocytopenia ($n = 5$; platelet count range 70 to $111 \times 10^3/\mu l$) did not affect the analyses.

Similar platelet counts were observed in patients who were medically treated ($n = 135$) and in patients who underwent surgery ($n = 57$) at day 1 ($182.6 \pm 114.1 \times 10^3/\mu l$ vs. $181.0 \pm 107.2 \times 10^3/\mu l$; $p = 0.93$) and day 8 ($304.2 \pm 149.1 \times 10^3/\mu l$ vs. $271.0 \pm 140.8 \times 10^3/\mu l$; $p = 0.16$). Day 8 platelet counts were lower in nonsurvivors than survivors regardless of whether they were medically treated ($190.7 \pm 111.9 \times 10^3/\mu l$ vs. $337.0 \pm 142.7 \times 10^3/\mu l$; $p < 0.001$) or surgically treated ($142.9 \pm 81.5 \times 10^3/\mu l$ vs. $303.8 \pm 134.3 \times 10^3/\mu l$; $p < 0.001$).

Infection with *Staphylococcus aureus* was associated with a lower mean platelet count at day 1 compared to nonstaphylococcal infections ($134.7 \pm 107.8 \times 10^3/\mu l$ vs. $223.7 \pm 98.4 \times 10^3/\mu l$; $p < 0.001$), but this association was not observed at day 8 ($307.8 \pm 172.3 \times 10^3/\mu l$ vs. $283.0 \pm 122.2 \times 10^3/\mu l$; $p = 0.28$). Older age, comorbidity (Charlson score), renal impairment, and hypoalbuminemia were associated with lower day 8 platelet counts ($p < 0.05$).

At day 1, the strongest univariate predictors of 6-month mortality by Cox proportional hazards regression analysis ($p \leq 0.01$) were Charlson score ≥ 3, echocardiographic left ventricular dysfunction, pulse rate, heart failure, and platelet count. At day 8, the strongest predictors were Charlson score ≥ 3, echocardiographic left ventricular dysfunction, heart failure, severe embolic event, intracardiac abscess, nonsinus rhythm, white cell count, platelet count, serum creatinine, and C-reactive protein.

Multivariate backward-stepwise Cox proportional hazards regression analysis incorporated univariate associations with $p < 0.10$ and other previously reported associations (2,3) with mortality with univariate $p \geq 0.10$ (Online Table 2). At baseline, platelet count ($p = 0.02$), age ($p = 0.006$), Charlson score ≥ 3 ($p = 0.006$), pulse rate ($p = 0.001$), congestive heart failure ($p = 0.004$), and serum creatinine ($p = 0.03$) were independent predictors. At day 8, platelet count ($p < 0.001$), congestive heart failure ($p = 0.01$), serum creatinine ($p = 0.04$), and severe embolic event ($p = 0.002$) were independent predictors. One limitation of our models is the relatively small number of events relative to the number of variables fitted. This mandates confirmation of the models in independent and larger cohorts.

To simplify its use as a clinical predictor, we assessed the relationship between thrombocytopenia (platelet count $<150 \times 10^3/\mu l$) and mortality. The incidence of thrombocytopenia was 45.1%, 33.3%, 16.2%, and 8.0% on days 1, 4, 8, and 12 respectively. Thrombocytopenia at presentation increased the odds of 6-month mortality 2.5-fold (95% confidence interval 1.3 to 4.6; $p = 0.004$), and thrombocytopenia at day 8 increased the odds 5.1-fold (95% confidence interval 2.7 to 9.8; $p < 0.001$).

Our study demonstrates that prognosis in infective endocarditis is related to the timing and severity of thrombocytopenia. Serial measurements of the platelet count may provide a simple means of monitoring the evolution of disease and the patient response to treatment in infective endocarditis.

Thrombocytopenia is likely to be a specific prognostic marker in endocarditis rather than simply a surrogate marker for the acute phase reaction. Platelets play an important role in the local host defense against endovascular infections, and experimentally induced thrombocytopenia is associated with more severe disease in animal models (1). Consistent with this, we found thrombocytopenia to be an independent predictor of mortality at both day 1 and 8. In contrast, acute phase reactants such as C-reactive protein and white cell count were univariate predictors of mortality but were

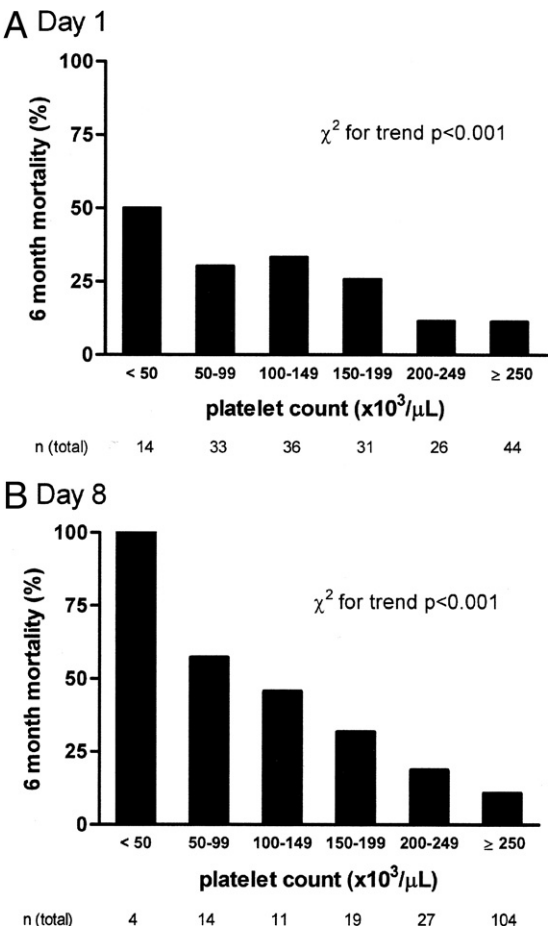

Figure 1 **Severity of Thrombocytopenia Is Associated With 6-Month Mortality**

Six-month mortality in relation to platelet count at day 1 **(A)** and at day 8 **(B)**. The total number of patients within each band of platelet counts is indicated by n. Chi-square test for trend $p < 0.001$ at day 1 and day 8.

not independently predictive on multivariate analysis. In addition, there was no association between erythrocyte sedimentation rate and mortality.

The finding of thrombocytopenia in patients with endocarditis has clinical implications. First, patients presenting with thrombocytopenia should receive empirical antistaphylococcal therapy because of the strong association between baseline thrombocytopenia and *Staphylococcus aureus* infection. Second, if antiplatelet agents are being considered as adjunctive therapy (4), clinicians should exclude coexistent thrombocytopenia because of its potential to increase the risk of bleeding. Third, thrombocytopenia at day 8 indicates an impaired host response to sepsis and predicts increased mortality. In this setting, patients with thrombocytopenia may warrant more intensive monitoring, alterations to treatment, and, where relevant, consideration of surgery.

Acknowledgments

The authors thank Dr. Tommy Chung and Associate Professor Jenny Peat for their assistance with statistical analyses.

Raymond W. Sy, MBBS
Chirapan Chawantanpipat, MBBS
David R. Richmond, MBChB, MSc
***Leonard Kritharides, MBBS, PhD**

*Department of Cardiology
3rd Floor West
Concord Repatriation General Hospital
Hospital Road, Concord
New South Wales
Australia, 2139
E-mail: lenk@med.usyd.edu.au

doi:10.1016/j.jacc.2008.01.034

Please note: Dr. Sy received a University of Sydney Postgraduate Award while undertaking this research.

REFERENCES

1. Sullam P, Frank U, Yeaman M, Tauber M, Bayer A, Chambers H. Effect of thrombocytopenia on the early course of streptococcal endocarditis. J Infect Dis 1993;168:910–4.
2. Hasbun R, Vikram HR, Barakat LA, Buenconsejo J, Quagliarello VJ. Complicated left-sided native valve endocarditis in adults: risk classification for mortality. JAMA 2003;289:1933–40.
3. Chu VH, Cabell CH, Benjamin DK Jr., et al. Early predictors of in-hospital death in infective endocarditis. Circulation 2004;109:1745–9.
4. Chan K, Dumesnil J, Cujec B, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. J Am Coll Cardiol 2003;42:775–80.

APPENDIX

For a supplementary figure and tables, please see the online version of this paper.

Letters to the Editor

Perioperative Myocardial Infarction Has Been Forgotten

Thygesen et al. (1) have published a consensus report that reviews the definition of myocardial infarction (MI) and proposes a new classification of 5 categories based on differences in pathophysiology. We believe that this definition is flawed in 1 respect: it does not mention perioperative MI. This is not the first time that a MI definition has been questioned. When the consensus document of the Joint European Society of Cardiology/American College of Cardiology redefinition of MI was released, Tunstall-Pedoe (2)