Early Predictors of In-Hospital Death in Infective Endocarditis

Vivian H. Chu, MD; Christopher H. Cabell, MD; Daniel K. Benjamin, Jr, MD, MPH, PhD; Erin F. Kuniholm, MD, MPH; Vance G. Fowler, Jr, MD, MHS; John Engemann, MD; Daniel J. Sexton, MD; G. Ralph Corey, MD; Andrew Wang, MD

Background—Data on early determinants of outcome in infective endocarditis (IE) are limited. We evaluated the prognostic significance of early clinical characteristics in a large, prospective cohort of patients with IE.

Methods and Results—Two hundred sixty-seven consecutive patients with definite or possible IE by modified Duke criteria and echocardiography performed within 7 days of presentation were evaluated. Acute physiology was assessed by the Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score at the time of presentation, and early heart failure was diagnosed by Framingham criteria. In-hospital mortality rate in the cohort was 19% and similar for patients with definite or possible IE (20% versus 16%, respectively; P=0.464). Independent predictors of death determined by logistic regression modeling were diabetes mellitus (OR 2.48; 95% CI, 1.24 to 4.96), Staphylococcus aureus as causative organism (OR, 2.06; 95% CI, 1.01 to 4.20), APACHE II score (OR, 1.07; 95% CI, 1.01 to 1.12), and embolic event (OR, 2.79; 95% CI, 1.15 to 6.80). Early echocardiographic findings of the Duke criteria were not predictive of death.

Conclusions—Early in the course of IE, readily available clinical characteristics that reflect the host-pathogen interaction are predictive of in-hospital death. These factors may identify those patients with IE for more aggressive treatment.

Key Words: endocardium ■ prognosis ■ infection ■ valves ■ echocardiography

Recent advances in the care of patients with infective endocarditis (IE) include improved diagnostic capability with the use of transesophageal echocardiography and more accurate diagnostic criteria. Despite these advances, IE remains a disease with a high mortality rate, in which patients with complications of IE may favor the opportunity to improve the outcome. Early identification of patients who are at high risk of death or complications of IE may offer the opportunity to improve the outcome of this disease.

Prior studies have evaluated predictors of death in IE. Wallace et al found that among clinical, microbiological, and echocardiographic features, only white blood cell count and serum albumin were independent predictors of short-term death. Cabell et al found an association between infection with Staphylococcus aureus and death. Recently, Hasbun et al derived a scoring system of clinical variables to predict 6-month survival in patients with complicated left-sided IE. These variables included comorbid illness, mental status, heart failure, causative organism, and surgical therapy. Finally, others have attempted to evaluate the prognostic role of echocardiography in IE, focusing on the association between vegetation size and risk of embolic events. The relation between echocardiographic findings and survival, however, remains undefined.

Previous studies have been limited by their retrospective nature. In addition, clinical and echocardiographic characteristics may change during an episode of IE because of the prolonged active phase and fluctuating course of this disease. Therefore, the objective of the present study was to determine factors early in the course of IE that were independently associated with death in a large cohort of prospectively identified patients. We also sought to evaluate whether early echocardiographic findings included in the Duke criteria were predictive of in-hospital death.

Methods

Patient Population

From 1996 to 2001, 351 consecutive patients with definite or possible IE according to modified Duke criteria were identified at a single tertiary-care medical center. Written informed consent was obtained from all participating patients, as required by the institutional review board under an approved protocol. Clinical, microbiological, and echocardiographic data of patients with definite or possible IE were collected prospectively in the Duke Endocarditis Database. For patients with repeat episodes of IE at our institution, only the first episode was included. To maintain a temporal relation between clinical, microbiological, and echocardiographic findings and to determine prognostic factors early in the course of IE, only...
patients who had an echocardiogram performed within 7 days of the initial hospital admission date (n=267) were included in this study.

Echocardiography
Transthoracic and/or transesophageal echocardiography as clinically indicated were performed as previously described.14–15 The presence of the following characteristics was determined: vegetation, abscess, new dehiscence, and new moderate or severe valvular regurgitation. A vegetation was defined as an irregularly shaped echogenic mass attached to a valve or myocardial surface.1 An abscess was defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance.1 Dehiscence was defined as a rocking motion of a prosthetic valve with an excursion of &gt;15° in at least one direction.1 For determination of severity of valvular regurgitation, semiquantitative analysis was performed with the use of color flow Doppler echocardiography and graded as none, trivial, mild, moderate, moderately severe, or severe. For the mitral and tricuspid valves, severity of regurgitation was analyzed on the basis of the area of the regurgitant jet relative to the area of the atrium.16 Aortic regurgitation severity was analyzed on the basis of the height of the regurgitant jet relative to the diameter of the left ventricular outflow tract.17

Data Collection
To control for severity of illness during the early active phase of IE, an Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score18 was calculated at the time of presentation to our institution. APACHE II is a validated scoring system that applies a weighted system of variables to predict the outcome of critically ill patients,18 with a range of 0 to 71 and a higher score representing a greater severity of illness. Heart failure during the initial 7 days of hospitalization was diagnosed by Framingham criteria.19

Analysis of Data
The primary outcome for this study was death during the index hospitalization for IE. Data are summarized as the mean±SD or number (percentage). Logistic regression analysis was performed to determine characteristics that were independently associated with death. Clinical, microbiological, and echocardiographic variables that were found to be significantly associated with death in bivariable analysis (P &lt;0.05) were included in the multivariable logistic regression analysis. To examine the association between organism and subsequent mortality, given sample size constraints, patients infected with S aureus were compared with a group including all other microbiological causes and culture-negative IE cases. The Statistical Analysis System (SAS Institute) and STATA 6.0/7.0 were used to perform the analyses.

Results
During the study period, 267 patients had definite or possible IE and were eligible for inclusion in this study: 188 (70%) patients had definite IE by Duke criteria. Most patients (82%) had native valve IE. The mean duration of symptoms before hospital admission was 9.6±7.3 days. For the entire cohort, the in-hospital mortality rate was 19%. The leading causes of death were sepsis (n=23, 46%), multi-organ failure (n=8, 16%), heart failure (n=4, 16%), and sudden death (n=4, 8%). Patients with definite IE by Duke criteria had an in-hospital mortality rate similar to those with possible IE (20% versus 16%, respectively; P =0.464).

Table 1 shows the bivariable comparison of patients with IE who survived to hospital discharge versus those who died. Male patients with IE had a significantly lower in-hospital mortality rate compared with female patients (OR, 0.42; 95% CI, 0.22 to 0.79). Patients with diabetes mellitus had a higher in-hospital mortality rate compared with non-diabetic patients (OR, 3.33; 95% CI, 1.77 to 6.27). A pathogenic organism was isolated from blood cultures in 236 patients (88%); S aureus was the most common causative organism (44%). Patients with IE caused by S aureus had a higher likelihood of in-hospital death (OR, 2.76; 95% CI, 1.46 to 5.23) than patients with other microbiological causes.

Echocardiographic Findings
Transthoracic echocardiography was performed in 241 patients (90%) and transesophageal echocardiography was performed in 176 patients (66%). Both modalities were performed in 153 patients (57%).

The echocardiographic findings as specified by the Duke criteria are shown in Table 1. A vegetation was evident by echocardiography in 62% of cases, with the majority of vegetations attached to a cardiac valve (95%). Among patients with IE who died during their hospitalization, 50% had aortic or mitral valve vegetations visualized compared with only 10% with evidence of right-sided vegetations. Echocardiographic evidence of an intracardiac abscess or prosthetic valve dehiscence was apparent in only a few cases (10% and 1%, respectively). New moderate or severe regurgitation, although seen in a high percentage of cases (36%), was similar between those who survived and those who died in the hospital.

Acute Physiology
There was a significant difference in total APACHE II score between in-hospital survivors versus deaths (11.1±6.6 versus 15.6±6.6, respectively; P &lt;0.001). This difference was due to the difference in the acute physiology component (5.9±4.9 versus 9.5±5.6, respectively; P &lt;0.001), with similar age and chronic health points (Table 1). Patients with S aureus IE had significantly higher APACHE II scores than patients with IE not caused by S aureus (14.7±7.0 versus 9.9±6.0, P &lt;0.001).

Clinical Events
The clinical events related to IE are depicted in Table 1. Heart failure during the initial 7 days of hospitalization occurred in 33% of patients and was associated with a trend toward higher mortality rates during the hospitalization in these cases (OR, 1.62; 95% CI, 0.86 to 3.05). Acute stroke at the time of admission was present in 14% of patients but was similar between in-hospital survivors and deaths (OR, 1.37; 95% CI, 0.56 to 3.30). In contrast, any stroke (at time of admission or during hospitalization) was associated with an increased risk of death (OR, 1.72; 95% CI, 0.85 to 3.49), and the occurrence of other embolic events (excluding stroke) was significantly more common in patients who died during the index hospitalization (OR, 2.92; 95% CI, 1.29 to 6.63). Cardiac surgery was performed in 27% of patients during their hospitalization, but in-hospital mortality rates were not significantly different between those who underwent cardiac surgery versus those who did not (14% versus 20%, respectively; P =0.321).

Predictors of Outcome
In the bivariable analyses, the factors associated with in-hospital death were diabetes mellitus, female gender, S aureus infection, APACHE II score, and embolic event (other
TABLE 1. Bivariable Association Between Patient Characteristics and In-Hospital Death

<table>
<thead>
<tr>
<th></th>
<th>Total (n=267)</th>
<th>Survived (n=217)</th>
<th>Died (n=50)</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±16</td>
<td>57±17</td>
<td>61±14</td>
<td>1.01</td>
<td>0.99–1.03</td>
<td>0.148</td>
</tr>
<tr>
<td>Male gender</td>
<td>148 (55)</td>
<td>129 (59)</td>
<td>19 (38)</td>
<td>0.42</td>
<td>0.22–0.79</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>88 (33)</td>
<td>60 (28)</td>
<td>28 (56)</td>
<td>3.33</td>
<td>1.77–6.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>18 (6)</td>
<td>14 (6)</td>
<td>4 (8)</td>
<td>1.26</td>
<td>0.40–4.01</td>
<td>0.694</td>
</tr>
<tr>
<td>HIV positive</td>
<td>8 (3)</td>
<td>5 (2)</td>
<td>3 (6)</td>
<td>2.71</td>
<td>0.62–11.7</td>
<td>0.183</td>
</tr>
<tr>
<td>Dialysis</td>
<td>77 (29)</td>
<td>61 (28)</td>
<td>16 (32)</td>
<td>1.20</td>
<td>0.62–2.33</td>
<td>0.584</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>48 (18)</td>
<td>42 (19)</td>
<td>6 (12)</td>
<td>0.56</td>
<td>0.22–1.42</td>
<td>0.225</td>
</tr>
<tr>
<td>Duration of symptoms, d</td>
<td>9.6±7.3</td>
<td>9.8±7.4</td>
<td>8.8±6.8</td>
<td>0.95</td>
<td>0.51–1.78</td>
<td>0.866</td>
</tr>
<tr>
<td>Transfer from other hospital</td>
<td>118 (44)</td>
<td>93 (43)</td>
<td>25 (50)</td>
<td>1.33</td>
<td>0.72–2.47</td>
<td>0.360</td>
</tr>
<tr>
<td>Organism isolated from blood culture</td>
<td>236 (88)</td>
<td>188 (87)</td>
<td>48 (96)</td>
<td>3.70</td>
<td>0.85–16.06</td>
<td>0.080</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>117 (44)</td>
<td>85 (39)</td>
<td>32 (64)</td>
<td>2.76</td>
<td>1.46–5.23</td>
<td>0.002</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>27 (10)</td>
<td>26 (12)</td>
<td>1 (2)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>23 (9)</td>
<td>18 (8)</td>
<td>5 (10)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>8 (3)</td>
<td>8 (4)</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
<td>28 (11)</td>
<td>24 (11)</td>
<td>4 (8)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>31 (11)</td>
<td>25 (12)</td>
<td>6 (12)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetation present</td>
<td>165 (62)</td>
<td>134 (62)</td>
<td>31 (62)</td>
<td>1.01</td>
<td>0.54–1.90</td>
<td>0.974</td>
</tr>
<tr>
<td>Aortic</td>
<td>36 (14)</td>
<td>27 (12)</td>
<td>9 (18)</td>
<td>1.62</td>
<td>0.71–3.72</td>
<td>0.252</td>
</tr>
<tr>
<td>Mitral</td>
<td>95 (36)</td>
<td>79 (36)</td>
<td>16 (32)</td>
<td>0.84</td>
<td>0.43–1.64</td>
<td>0.621</td>
</tr>
<tr>
<td>Tricuspid</td>
<td>23 (9)</td>
<td>19 (9)</td>
<td>4 (8)</td>
<td>0.95</td>
<td>0.31–2.92</td>
<td>0.925</td>
</tr>
<tr>
<td>Pulmonic</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Abscess</td>
<td>28 (10)</td>
<td>21 (10)</td>
<td>7 (14)</td>
<td>1.52</td>
<td>0.61–3.80</td>
<td>0.525</td>
</tr>
<tr>
<td>New dehiscence</td>
<td>3 (1)</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td>2.19</td>
<td>0.20–24.68</td>
<td>0.636</td>
</tr>
<tr>
<td>New moderate or severe regurgitation</td>
<td>97 (36)</td>
<td>77 (36)</td>
<td>20 (40)</td>
<td>1.20</td>
<td>0.64–2.26</td>
<td>0.565</td>
</tr>
<tr>
<td>APACHE II Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>12.0±6.9</td>
<td>11.1±6.6</td>
<td>15.6±6.6</td>
<td>1.10</td>
<td>1.05–1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute physiology points</td>
<td>6.6±5.2</td>
<td>5.9±4.9</td>
<td>9.5±5.6</td>
<td>1.12</td>
<td>1.07–1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age points</td>
<td>2.9±1.4</td>
<td>2.8±1.4</td>
<td>3.1±1.3</td>
<td>1.17</td>
<td>0.94–1.46</td>
<td>0.154</td>
</tr>
<tr>
<td>Chronic health points</td>
<td>1.5±0.5</td>
<td>1.5±0.5</td>
<td>1.5±0.5</td>
<td>1.38</td>
<td>0.74–2.55</td>
<td>0.312</td>
</tr>
<tr>
<td>Clinical events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early heart failure</td>
<td>88 (33)</td>
<td>67 (31)</td>
<td>21 (42)</td>
<td>1.62</td>
<td>0.86–3.05</td>
<td>0.133</td>
</tr>
<tr>
<td>Stroke at presentation</td>
<td>39 (15)</td>
<td>30 (14)</td>
<td>9 (18)</td>
<td>1.37</td>
<td>0.56–3.30</td>
<td>0.595</td>
</tr>
<tr>
<td>Any stroke</td>
<td>54 (20)</td>
<td>40 (18)</td>
<td>14 (28)</td>
<td>1.72</td>
<td>0.85–3.49</td>
<td>0.132</td>
</tr>
<tr>
<td>Other systemic emboli</td>
<td>30 (11)</td>
<td>19 (8)</td>
<td>11 (22)</td>
<td>2.92</td>
<td>1.29–6.63</td>
<td>0.010</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>71 (27)</td>
<td>61 (28)</td>
<td>10 (20)</td>
<td>0.64</td>
<td>0.30–1.36</td>
<td>0.245</td>
</tr>
</tbody>
</table>

Values are n (%) or mean±SD. than stroke). When these variables were analyzed by multivariable logistic regression (Table 2), diabetes mellitus, *S. aureus* IE, APACHE II score, and embolic event remained independently associated with in-hospital death (area under receiver operating characteristic curve, 0.75). When included in the multivariable analysis, cardiac surgery was not an independent predictor of outcome (P=0.763) and did not alter the point estimates of the other variables in the model.

**Discussion**

Clinicians caring for patients with IE need to be able to accurately identify patients who are at highest risk for death early in the course of their illness. The utility of the Duke criteria⁴ for the diagnosis of IE is clear, but the potential prognostic role of this information has not been well defined. One challenging aspect of this disease is the dynamic nature of clinical, microbiological, and echocardiographic findings in the active phase of IE. Our study demonstrates that clinical factors that are apparent early in the course and reflective of the host-pathogen relation predict in-hospital death. Recognition of these factors may improve risk stratification and allow for more intensive treatment of these patients.

The present study was unique in several ways. Our relatively large cohort was defined by the Duke criteria⁵ in a contemporary period, reflective of the changing characteristics of this disease.⁶ Clinical and echocardiographic data were
collected prospectively and focused on a discrete time interval (initial 7 days of hospitalization at a single institution). To our knowledge, this is the first study of IE to diagnose the presence of heart failure by validated criteria.

Our study was also the first to assess acute physiology in patients with IE and evaluate its relation to outcome. Measurement of the APACHE II score at the time of admission allowed the current investigation to adjust for important clinical characteristics. As a predictor of in-hospital death, the acute physiology score emphasizes that the early systemic effects of IE have significant prognostic implications. The duration of symptoms before hospital admission was relatively short and similar between those patients who survived versus those who died, suggesting that a higher acute physiology score was not related to delayed presentation.

Patients with *S aureus* as the causative organism had a higher likelihood of in-hospital death. *S aureus* was the most common organism (44%) in this study, and the percentage of *S aureus* IE cases continues to increase.2,20 This organism has been associated with both a higher rate of complications11,21 and mortality in IE.10,12,21,22 Earlier intervention before the development of complications may offer greater benefit for these patients.

Interestingly, diabetes mellitus, which had a high prevalence in our cohort (33%), was associated with a 2-fold greater likelihood of in-hospital death in IE. Few studies have evaluated diabetes mellitus as a risk factor in IE, but a recent study found a nonsignificant trend toward higher in-hospital mortality rates among patients with diabetes (36% versus 16%).21 The higher mortality rates in patients with diabetes mellitus may be related to the adverse effects of hyperglycemia on immune function.24,25 A recent randomized, controlled trial showed that intensive control of hyperglycemia with insulin therapy, regardless of diabetic status, reduced the mortality rate in critically ill patients.26 Whether improved glycemic control in patients with IE has a beneficial effect on outcome remains to be studied.

Specific echocardiographic findings of the Duke criteria assessed early in the course of IE were not predictive of in-hospital death. Other studies evaluating the prognostic role of echocardiography in IE have had inconsistent results. Indeed, the presence of a vegetation in *S aureus* IE has been associated with a lower mortality rate compared with patients without vegetation visualized by echocardiography.25 Classification as definite IE rather than possible IE (primarily as a result of the echocardiographic findings) was also not associated with poorer outcome. These results may reflect changing echocardiographic findings during the course of IE, such that echocardiography may have greater diagnostic utility than prognostic significance in early IE.

Prior studies have evaluated the ability of echocardiography to predict complications of IE. Vegetation size and mobility have been found to be predictors of embolic events in some studies.11,13 Jaffe et al12 reported a trend toward a higher risk of embolization in patients with vegetations >10 mm; however, echocardiographic characteristics of vegetations did not predict death. Although the present study did not evaluate vegetation size or mobility, embolic events may represent a mechanistic variable linking vegetation size and outcome.

Embolic events are well-recognized complications of IE, occurring in ~30% to 40% of left-sided IE cases.27,28 Previous studies have shown that the incidence of embolic events was highest early in the course of IE, typically before or during the first 2 weeks of antibiotic therapy.27,28 The results of this study emphasize the prognostic significance of these early events. Whereas recurrent embolic events has been a recognized indication for surgical intervention in IE,29 our findings suggest that any embolic event should be regarded as an indicator of increased death risk.

Early heart failure as defined by the Framingham criteria was present in one third of this cohort but was not independently associated with in-hospital death. The timing of heart failure in the course of IE may influence its prognostic significance. Roder et al22 found that the presence of heart failure early in the disease process was not associated with higher mortality rates, whereas late heart failure was associated with poorer survival. Heart failure has been shown to be a prognostic factor in other studies10,30; however, in these studies, the method used to diagnose heart failure was not defined. As a result, diagnostic heterogeneity may have influenced the results,31 with potential bias toward more severe heart failure. The Framingham criteria may be sensitive for the detection of mild heart failure or heart failure unrelated to IE, thus limiting its prognostic ability for a short-term end point.

Cardiac surgery for IE, performed in 27% of patients during their index hospitalization, was not associated with lower in-hospital mortality rates in this study. In contrast, Hasbun et al10 found that cardiac surgery was an independent predictor of 6-month survival in a subset of patients with complicated left-sided IE. Hoen et al7 found that despite a higher percentage of IE cases caused by *S aureus* in a 10-year interval, in-hospital mortality rates decreased and may have been related to a higher rate of cardiac surgery. In both of these studies, rates of cardiac surgery (45% and 50%, respectively) were significantly higher than in the present study. To date, no randomized, controlled studies of cardiac surgery for IE have been performed, and both referral and selection biases may influence the rates and observed effects of surgery in different cohorts. Currently, cardiac surgery is recommended predominantly for complications of IE, such as recurrent embolic events, heart failure unresponsive to medical therapy, or evidence of perivalvular extension.29 Further studies are needed to evaluate whether earlier surgical intervention for patients at higher risk of death will improve outcome.
This study has several limitations. It is subject to the referral bias of a large tertiary-care center, as illustrated by the proportion of patients transferred from community hospitals and the high percentage *S. aureus* infection. Because the study was conducted at a single center, regional variation in the diagnosis and treatment of IE may have influenced results. Transesophageal echocardiography was performed as clinically indicated in 66% of the cohort; higher utilization may have altered the echocardiographic findings and their relation to outcome. However, subset analysis of those patients who had transesophageal echocardiograms found no association between echocardiographic findings of the Duke criteria and in-hospital death. Vegetation size was not prospectively collected or evaluable in this database, but the presence of a vegetation was not predictive of worse outcome compared with those without vegetation visualized. Finally, acute physiology and heart failure were ascertained retrospectively, and detection bias could have occurred as a result.

In conclusion, factors indicative of the host-pathogen interaction in IE—diabetes mellitus, *S. aureus* infection, acute physiological severity, and embolic events—are early, independent determinants of in-hospital death. Early echocardiographic information, though useful diagnostically, did not predict outcome. These findings offer a means of early risk stratification of patients with IE and thus may identify higher-risk patients for more aggressive treatment or interventions.

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References
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