Waiting for Microbiologic Data to Direct Therapy Against Nosocomial Infections in Febrile Surgical Patients

Are Outcomes Worsened?

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Hypothesis: Allowing adequate time for laboratory and culture results before initial treatment may be associated with a worse outcome in nosocomial infections.


Setting: Surgical services at a university hospital.

Patients and Methods: In surgical patients presenting with fever, 372 episodes of nosocomial infection were evaluated. Nosocomial infections were divided by time from fever to intervention (≤12, 13-24, and >24 hours). These groups were subdivided by Acute Physiology and Chronic Health Evaluation II (APACHE II) scores into low (≤10 [n=114]), moderate (11-20 [n=169]), and high severity of illness (>20 [n=89]). Pneumonia and bloodstream infections were divided by APACHE II scores into low (≤15 [n=55 and n=56, respectively]) or high severity of illness (>15 [n=84 and n=77, respectively]).

Main Outcome Measures: Mortality, length of stay.

Results: No difference in outcome was seen between different time intervals from fever to intervention for nosocomial infections in patients with APACHE II scores of no more than 10. Patients treated more than 24 hours after fever were significantly younger than those treated at no more than 12 and 13 to 24 hours with APACHE II scores of 11 to 20 (P<.05) and more than 20 (P<.05). Mortality and length of stay for patients treated at later time intervals were comparable with those of patients treated earlier with similar APACHE II scores. There was no difference in outcome for patients with pneumonia or bloodstream infection.

Conclusions: Episodes of infection in which treatment was withheld until initial microbiologic data were available (24 hours) did not have worse outcomes compared with those treated earlier. Waiting for laboratory and culture results to direct antibiotic therapy for nosocomial infections does not appear harmful and may be potentially beneficial.

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INFECTIOUS complications are a notable source of morbidity and mortality in surgical patients. Because of toxic side effects and expense of antibiotics and resistance as a consequence of excessive or inappropriate use,1,2 the optimal timing and choice of antibiotic therapy for suspected infection is unclear. Although conflicting reports exist,3,4 studies have demonstrated appropriate and timely therapy to be associated with decreased mortality rates.3,4 These studies imply that waiting for microbiologic tests before implementing therapy may have deleterious effects on patient survival.

A physician’s clinical experience is the most common justification for implementing empiric antimicrobial therapy,6 but this may lead to misinformation about potential pathogens and susceptibilities.7,8 Computerized antibiotic consultation has been demonstrated to improve antibiotic selection,8,9 but it may not be practical in all settings and has less value for determining when to initiate empiric treatment. Because of the numerous confounding factors of empiric antibiotic therapy, the availability of important data, including laboratory results, Gram stain, and preliminary cultures, may allow more directed therapy, limit adverse effects, and improve outcome. Preliminary microbiologic results should be available within 24 hours of initial evaluation for suspected infection. At present, the effect on outcome of waiting for this information is unknown.4

Severity of infection10 and underlying illness11 have been demonstrated to be key determinants of survival after gram-negative bacteremia. Therefore, patients with minimal underlying disease may be expected to have acceptable outcomes despite delayed intervention. Likewise, those with severe underlying illness may do poorly despite early and appropriate therapy. Improvements in outcome from timely and directed therapy may be greatest in patients with moderate underlying illness.

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PATIENTS AND METHODS

PATIENTS AND DATA COLLECTION

This study was approved by the University of Virginia Human Investigation Committee, Charlottesville. All episodes of infection occurring from December 10, 1996, to October 28, 1998, in patients on the general, trauma, and transplant surgery services at the University of Virginia Health Sciences Center were prospectively evaluated. Data were collected every other day by chart review, interview of hospital personnel, and patient evaluation. Criteria for entry into the study included the initiation of treatment resulting from isolation of a predominant organism from a normally sterile site using standard culture techniques or presumptive diagnosis of infection with high probability of leading to therapy (eg, wound infection). Treatment included use of antimicrobials, percutaneous or surgical drainage, or removal of foreign body or hardware. Only nosocomial infections associated with fever before treatment were evaluated to allow calculation of the time from febrile illness to initiation of antibiotics.

Variables recorded included age, sex, patient location at time of initial treatment (eg, intensive care unit [ICU], home, hospital ward), primary diagnosis and operations, comorbidities (eg, diabetes, coronary artery disease, renal insufficiency, dialysis, pulmonary disease, need for mechanical ventilation, malignant neoplasm, steroid use, transplantation), maximum temperature, time of infection, a series of consecutive infections were studied among hospitalized surgical patients in a tertiary care center. Outcomes were analyzed from episodes of infection stratified by time to initial intervention and further subdivided by severity of illness.

RESULTS

ALL INFECTIONS

Of 1335 total episodes of infection recorded during the study period, 372 (27.9%) in 274 patients were nosocomial infections presenting with fever before treatment. Characteristics and outcomes for episodes of infection occurring in patients with APACHE II scores from 11 to 20 and of more than 20 are summarized in Table 1. No differences were noted in those with APACHE II scores of no more than 10 (data not shown). Age was lower for those treated after 24 hours in moderate and severe illness. Early empiric therapy (≤12 hours) was not associated with decreased mortality in any group (Figure 1). Patients with APACHE II scores from 11 to 20 had a lower mortality when antibiotic therapy was initiated at 13 to 24 hours (2.0%) compared with more than 24 hours (16.7%; P = .01). In patients with APACHE II scores of more than 20, mortality was lower when treatment was instituted more than 24 hours after fever (16.7%) compared with no more than 12 hours (41.7%; P = .054). Length of stay after the diagnosis and institution of treatment was similar in all groups with similar APACHE II scores.

For nosocomial infections in surgical patients presenting with fever and APACHE II scores of no more than 10, sites of infection, antibiotics administered, and distribution of infecting organisms were similar (data not shown). Sites of infection, antibiotics administered, and distribution of infecting organisms for infections occurring in patients with APACHE II scores from 11 to 20 and of more than 20 are demonstrated in Figure 2. For those with APACHE II scores from 11 to 20, a greater proportion of peritoneal infections were treated within 12 hours (16.3%) compared with more than 24 hours (3.4%; P = .01). For those with APACHE II scores of more than 20, a greater percentage of central line infections were treated from 13 to 24 hours (22.2%) compared with no more than 12 hours (8.6%; P = .04). All other sites infected were similar between groups (Figure 2, A). Distribution of infecting organisms and antibiotics administered were similar for groups with APACHE II scores from 11 to 20 (Figure 2, B and C). Episodes of infection occurring in those with APACHE II scores of more than 20 and treated more than 24 hours after onset of fever were associated with a greater proportion of gram-positive organism (58.7%) compared with those treated no more than 12 hours and within 13 to 24 hours (34.6% and 32.6%; P = .006 and P = .01, respectively) (Figure 2, C). Reciprocally, the incidence of gram-negative organisms was lower in those with severe illness treated more than 24 hours after the onset of fever compared with those treated within 13 to 24

Continued on next page
antibiotic choice was determined by resistance of a cultured organism to the prescribed antimicrobial regimen. Patients with a presumptive diagnosis of infection with high probability of leading to therapy but without definitive culture results as well as patients with central venous catheter infections treated by removal of the catheter without antimicrobial therapy were excluded from analysis of appropriate antibiotic therapy.

SEVERITY OF ILLNESS

The Acute Physiology Score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score\textsuperscript{16} were used as markers for severity of illness. For all nosocomial infections presenting with fever, an APACHE II score of no more than 10 was defined as minimal illness; from 11 to 20, moderate illness; and of more than 20, severe illness.

Nosocomial pneumonia and bloodstream infection (BSI) in patients presenting with fever were analyzed separately. To maintain adequate group sizes, both were separated into only 2 groups: APACHE II score of no more than 15 for minimal to moderate illness and more than 15 for more severe illness.

INFECTION CRITERIA

Criteria for identification of nosocomial infection included any infection occurring in hospitalized patients that was not suspected on admission.\textsuperscript{11} Pneumonia was defined as the presence of copious sputum production, systemic evidence of infection (fever or leukocytosis), and isolation of a single predominant organism in association with a new or changing pulmonary infiltrate on chest radiography. Bloodstream infection was defined as isolation of organisms from a single blood culture drawn seriatim, with the exception of Staphylococcus epidermidis or coagulase-negative Staphylococcus species, which required isolation from 2 sites. Urinary tract infection criteria required the presence of more than 10\textsuperscript{5} colony-forming units (cfu)/mL of urine, or more than 10\textsuperscript{4} cfu/mL of urine with typical clinical signs and symptoms. The presence of wound infections, peritonitis, and cellulitis was determined using clinical evaluation, frequently without culture. Catheter infection was diagnosed by the presence of at least 15 cfu of bacteria on catheter tip culture. Catheters were only cultured when suspected of infection (localized purulence or systemic evidence of infection).

Infections occurring in the same patient more than 72 hours apart were considered separate episodes and analyzed individually.

STATISTICAL ANALYSIS

Values are expressed as mean ± SE. Analysis of categorical data was performed using $\chi^2$ testing. Continuous data were analyzed using analysis of variance with post hoc analysis with the Tukey Kramer test. A $P$ value of less than .05 was considered significant. Calculations were performed using statistical software (GB-STAT, version 6.5; Dynamic Microsystems Inc, Silver Spring, Md).

hours (23.9% vs 44.2%, respectively; $P = .04$). Most likely as a result, vancomycin hydrochloride use was highest in the group treated after more than 24 hours (Figure 2, B). Etiologic organisms were cultured from 76.8% of all nosocomial infections presenting with fever in surgical patients. For patients with minimal illness treated at no more than 12, 13 to 24, and more than 24 hours after the onset of fever, there was no difference in the proportion receiving initial appropriate therapy (75.0%, 65.2%, and 72.7%, respectively; $P = .43$). The mean time to appropriate therapy in patients with APACHE II scores of no more than 10 was significantly longer for episodes of infection initially treated more than 24 hours after febrile illness compared with those treated within 12 hours (2.3 ± 0.2 vs 0.3 ± 0 days; $P = .01$). The evaluation for appropriateness of antimicrobial therapy in moderate and severe illness is presented in Table 2.

<table>
<thead>
<tr>
<th>Table 1. Characteristics and Outcomes of All Nosocomial Infections in Surgical Patients Presenting With Fever*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interval From Fever to Treatment, h</strong></td>
</tr>
<tr>
<td>No. of episodes</td>
</tr>
<tr>
<td>Fever to treatment, h</td>
</tr>
<tr>
<td>APACHE II score</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Male, %</td>
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<tr>
<td>WBC, (10^9/L)</td>
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<tr>
<td>Maximum temperature, °C</td>
</tr>
<tr>
<td>Length of stay, d</td>
</tr>
<tr>
<td>Time to defervescence, d</td>
</tr>
<tr>
<td>Days to WBC &lt;15 (10^9/L)</td>
</tr>
<tr>
<td>Total days of antibiotics</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SE. APACHE II indicates Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell count.

\(\ddagger P = .01\) vs 0 to 12 hours.

\(\ddagger P = .05\) vs 13 to 24 hours.

\(\ddagger P = .04\) vs 0 to 12 hours.

\(\ddagger\ddagger P = .01\) vs 0 to 12 hours.

\(\ddagger\ddagger\ddagger P = .04\) vs 0 to 12 hours.

\(\ddagger\ddagger\ddagger\ddagger P = .05\) vs 13 to 24 hours.

\(\ddagger\ddagger\ddagger\ddagger\ddagger P = .01\) vs 0 to 12 hours.

\(\ddagger\ddagger\ddagger\ddagger\ddagger\ddagger P = .04\) vs 0 to 12 hours.

\(\ddagger\ddagger\ddagger\ddagger\ddagger\ddagger\ddagger P = .05\) vs 13 to 24 hours.
Although the appropriateness of antibiotic therapy was similar for those with moderate illness, patients with APACHE II scores of more than 20 receiving therapy from 13 to 24 hours after fever initially were treated more appropriately than those treated at no more than 12 hours (90.5% vs 65.9%; \( P = .04 \)). However, the mean time to appropriate therapy was similar (1.4 ± 0.3 vs 0.9 ± 0.2 days; \( P = .15 \)). The time to appropriate therapy was significantly longer in all groups receiving therapy more than 24 hours after the onset of fever. Only 4 episodes of infection (1.1%) continued to receive inappropriate or no therapy after the availability of culture data.

**PNEUMONIA AND BSI**

One hundred thirty-nine episodes of nosocomial infection (37.4%) were of the lung. Characteristics and outcomes for patients with lesser and severe illness (are summarized in Table 3). Patients with severe illness treated more than 24 hours after the onset of fever were younger compared with those treated at no more than 12 and from 13 to 24 hours (38 ± 4 vs 54 ± 2 and 54 ± 4 years, respectively; \( P = .01 \)). All other characteristics, including severity of illness, mortality, length of stay, resolution of leukocytosis, and time to defervescence were similar for those treated at different time intervals when grouped by APACHE II scores. Antimicrobial use was similar between time intervals of treatment for those with less severe illness. Severe illness treated within 13 to 24 hours from onset of fever was associated with an increased use of fluoroquinolones (21.4%) compared with those treated within 12 hours (9.6%; \( P = .02 \)). In patients with APACHE II scores of less than 15, gram-positive lung organisms were more common in the group treated within 12 hours from the onset of fever (23.7%) compared with those treated after more than 24 hours (0%; \( P = .053 \)). However, there was no statistical difference in mortality between all episodes of gram-positive cocci pneumonia (23/95 [24.2%]) compared with those without gram-positive cocci (6/44 [13.6%]; \( P = .15 \)). Otherwise, all other organisms were similar between different time intervals of treatment.

Organisms were cultured in 61.2% of all episodes of nosocomial pneumonia presenting with fever. All other episodes of pneumonia included the presence of mixed organisms or indeterminate cultures in the setting of aspiration. An evaluation of therapeutic appropriateness for pneumonia is presented in Table 4. The time to appropriate therapy was significantly longer for patients with APACHE II scores of no more than 15 and more than 15 who were treated more than 24 hours after febrile illness compared with those treated at earlier time intervals.

Of 372 nosocomial infections presenting with fever, 133 (35.6%) included BSI. Characteristics and outcomes are summarized in Table 5. There was no difference in mortality for those treated at later time intervals with similar severity of illness. Those with severe illness (APACHE II score, >15) and treated more than 24 hours after the onset of fever were younger (37 ± 3 years) than those treated at earlier time intervals (≤12 hours, 56 ± 2 years [\( P = .01 \)]; and 13-24 hours, 51 ± 4 years [\( P = .051 \)]. For episodes of nosocomial BSI presenting with fever, concurrent sites were similar and included peritonitis (5.2%), lung (18.3%), catheter (11.2%), urine (8.6%), and wound infections (4.5%). Differences in organisms from blood cultures are illustrated in Figure 3. Gram-positive cocci were the most common pathogens isolated.

An evaluation of therapeutic appropriateness for BSI is presented in Table 4. Patients with mild to moderate illness treated within 13 to 24 hours after fever were less likely to receive appropriate antibiotic regimens compared with those treated at no more than 12 or more than 24 hours after fever (56.3% vs 88.9% [\( P = .01 \)] and 91.7% [\( P = .04 \)], respectively). The appropriateness of initial therapy was similar for patients with APACHE II scores of more than 15. The time to appropriate therapy was significantly longer for infections treated at later time intervals compared with those with initial early intervention.

**COMMENT**

Nosocomial infections continue to be a source of morbidity and mortality in surgical patients. The optimal time for institution of antimicrobial therapy for suspected infection remains unclear. The effect of delaying intervention to allow possible directed therapy based on microbiologic data was analyzed. Delayed therapy was not associated with an increased mortality or length of stay in patients with similar severity of illness. Instead, therapy implemented at later time intervals was associated with similar or decreased crude mortality rates. These findings suggest waiting for microbiologic data before initiating therapy is not harmful, and may be beneficial.

In the early intervention group, the process involving patient evaluation, antibiotic ordering, pharmacy preparation, and medication administration would likely have consumed much of the time before intervention. Therefore, little laboratory data would be expected to have been available at the initial time of choosing empiric therapy. In contrast, patients treated at moderate time intervals, receiving treatment on average more than 20 hours after the onset of fever, would have
received therapy after the availability of Gram stains and preliminary cultures. The value of waiting for early microbiologic results is supported by a study in which Gram stain of expectorated sputum to guide treatment of community-acquired pneumonia led to appropriate antibiotic therapy in 94% of cases. A second study demonstrated Gram stain of tracheal aspirations from patients in a surgical ICU that were positive for gram-negative rods correlated with 89% of culture results opposed to only 33% of cultures yielding gram-positive cocci. In our study, antibiotics prescribed late after the onset of fever were clearly done so with the knowledge

Table 2. Evaluation of Appropriateness of Antimicrobial Therapy for Nosocomial Infections in Surgical Patients Presenting With Fever

<table>
<thead>
<tr>
<th>Interval From Fever to Treatment, h</th>
<th>APACHE II Score, 11-20</th>
<th>APACHE II Score, &gt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-12</td>
<td>13-24</td>
</tr>
<tr>
<td>Episodes with organism cultured, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial therapy appropriate, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to appropriate therapy, mean ± SE, d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*APACHE II indicates Acute Physiology and Chronic Health Evaluation II.
†P = .04 vs 0 to 12 hours.
‡P = .01 vs 0 to 12 and 13 to 24 hours.
§P = .01 vs 0 to 12 hours.
of some speculation and sensitivity data in 76.8% of cases. Similar to the previously reported 30% to 50%, 21-23 a definitive microbiologic diagnosis remained unknown in 23.2% of episodes of infection. In our study, initiation of therapy at later time intervals was not related consistently with improved antimicrobial selection.

The data generated from our study need to be interpreted with caution. Although the total number of episodes of infection is moderately large, the subgroups analyzed were at times considerably smaller and should be reanalyzed in larger studies. This is particularly true for the severely ill patients, in whom differences in outcome tend to be small and difficult to prove, no matter the intervention. In addition, an insufficient sample size may have been present, limiting the ability to detect a difference in mortality within the subgroups of nosocomial pneumonia and BSI. However, a large difference in mortality was not associated consistently with delays in therapeutic intervention. Instead, mortality rates were often similar and, in some cases, tended to decrease with later time intervals.

The stratification schema was effective in our study. The mean APACHE II scores were well matched when patients were subgrouped by severity of illness. In addition, the arbitrary division of time from fever to treatment appeared to be clinically relevant. The mean times to therapy for the early- (approximately 6 hours), middle- (approximately 22 hours), and late-treatment groups (approximately 55 hours) were clearly different and represent time intervals when increasing microbiologic information would be available.

Similar or improved survival for nosocomial infections treated at later time intervals from the onset of fever may result from a single or a combination of several possibilities. A physician bias toward treating healthier or younger patients at later time intervals may exist. Severity of illness was controlled for in our study by grouping patients by APACHE II scores. Delayed therapy was associated with a younger age. Earlier intervention in older patients may have been instituted because increasing age is associated with worse outcomes from infectious complications. However, early intervention has not been clearly demonstrated to im-

Table 3. Characteristics and Outcomes of Pneumonia in Surgical Patients Presenting With Fever*

<table>
<thead>
<tr>
<th>Interval From Fever to Treatment, h</th>
<th>APACHE II Score, ≤15</th>
<th>APACHE II Score, &gt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-12</td>
<td>13-24</td>
</tr>
<tr>
<td>No. of episodes</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>Fever to treatment, h</td>
<td>6 ± 1</td>
<td>22 ± 1</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>11 ± 1</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>Age, y</td>
<td>42 ± 3</td>
<td>44 ± 5</td>
</tr>
<tr>
<td>Male, %</td>
<td>64.3</td>
<td>68.7</td>
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<tr>
<td>WBC, ×10^9/L</td>
<td>13.1 ± 1.0</td>
<td>16.0 ± 2.2</td>
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<tr>
<td>Maximum temperature, °C</td>
<td>38.9 ± 0.1</td>
<td>39.0 ± 0.1</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>3.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>21 ± 3</td>
<td>19 ± 9</td>
</tr>
<tr>
<td>Time to defervescence, d†</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Days to WBC &lt;15 × 10^9/L</td>
<td>3 ± 1</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Total days of antibiotics</td>
<td>12 ± 1</td>
<td>11 ± 1</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SE. APACHE II indicates Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell count.
†P = .01 vs 0 to 12 hours
‡Defined as days until temperature lower than 38°C for 24 consecutive hours.

Table 4. Evaluation of Appropriateness of Antimicrobial Therapy for Pneumonia and Bloodstream Infection in Surgical Patients Presenting With Fever*

<table>
<thead>
<tr>
<th>Interval From Fever to Treatment, h</th>
<th>APACHE II Score, ≤15</th>
<th>APACHE II Score, &gt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-12</td>
<td>13-24</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes with organism cultured, %</td>
<td>46.4</td>
<td>43.8</td>
</tr>
<tr>
<td>Initial therapy appropriate, %</td>
<td>78.6</td>
<td>68.8</td>
</tr>
<tr>
<td>Time to appropriate therapy, mean ± SE, d</td>
<td>1.0 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial therapy appropriate, %</td>
<td>88.9</td>
<td>56.3</td>
</tr>
<tr>
<td>Time to appropriate therapy, mean ± SE, d</td>
<td>0.7 ± 0.2</td>
<td>1.9 ± 0.3†</td>
</tr>
</tbody>
</table>

*APACHE II indicates Acute Physiology and Chronic Health Evaluation II.
†P < .02 vs 0 to 12 and 13 to 24 hours.
‡By definition, all episodes of bloodstream infection were associated with a cultured organism(s).
§P < .02 vs 0 to 12 and P < .04 vs >24 hours.
|P < .05 vs 0 to 12 hours.
prove outcome, whereas our study demonstrates that delayed treatment is not associated with worse outcomes. Wrong or inappropriate empiric therapy early after diagnosis may have a similar effect to receiving no therapy until directed by culture data. Studies demonstrate antibiotic misuse to range from 41% to 66% at university medical centers,

Wrong or inappropriate empiric therapy early after diagnosis may have a similar effect to receiving no therapy until directed by culture data. Studies demonstrate antibiotic misuse to range from 41% to 66% at university medical centers, and empiric therapy may be based on misinformation about potential pathogens and susceptibilities.

Bryan et al demonstrated that inappropriate or no therapy had similar outcomes for gram-negative bacteremia compared with effective initial empiric therapy if both of the former were correctly adjusted based on cultures. In contrast, a higher mortality was seen in patients not treated at all or never treated appropriately. Interestingly, Schiffman et al demonstrated that appropriate therapeutic changes were performed by physicians on the medicine service in 50% of cases within 48 hours of the availability of a discrepancy between antibiotic therapy and results of antimicrobial susceptibility tests without intervention by the study group compared with 0% on surgery services.

In our study, differences in mortality were not associated with delays in appropriate treatment. The therapeutic regimens of only a small cohort (1.1%) were not appropriate initially or were not changed to appropriate therapy based on results of antimicrobial sensitivity tests. This may be a result of the considerable emphasis on surgical infectious complications and their treatment at our institution. Studies have demonstrated that efficient reporting of results of antimicrobial susceptibility tests can lead to more appropriate and cost-effective antibiotic therapy.

Figure 3. Distribution of infecting organisms for episodes of nosocomial bloodstream infection in surgical patients presenting with fever. Comparison is made by time from fever to treatment in patients with minimal to moderate (Acute Physiology and Chronic Health Evaluation II [APACHE II] score, \( \leq 15 \)) (A) and severe illness (APACHE II score, >15) (B). Asterisk indicates \( P = .005 \) vs delays of 13 to 24 hours; dagger, \( P = .04 \) vs delays of 13 to 24 hours; double dagger, \( P = .02 \) vs delays of more than 24 hours; section mark, \( P = .007 \) vs delays of more than 24 hours; and other, no culture obtained, no growth, mixed flora, etc.

Table 5. Characteristics and Outcomes of Bloodstream Infection in Surgical Patients Presenting With Fever

<table>
<thead>
<tr>
<th>Interval From Fever to Treatment, h</th>
<th>APACHE II Score, ( \leq 15 )</th>
<th>APACHE II Score, &gt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-12</td>
<td>13-24</td>
</tr>
<tr>
<td>No. of episodes</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Fever to treatment, h</td>
<td>8 ± 1</td>
<td>21 ± 1</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
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<tr>
<td>Age, y</td>
<td>47 ± 3</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>Male, %</td>
<td>55.6</td>
<td>58.8</td>
</tr>
<tr>
<td>WBC, ( \times 10^9/\text{L} )</td>
<td>14.0 ± 1.3</td>
<td>12.5 ± 1.4</td>
</tr>
<tr>
<td>Maximum temperature, °C</td>
<td>39.0 ± 0.1</td>
<td>39.0 ± 0.2</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>7.4</td>
<td>0</td>
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<tr>
<td>Length of stay, d</td>
<td>24 ± 8</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>Time to defervescence, d</td>
<td>2.3 ± 0.8</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Days to WBC &lt;15 ( \times 10^9/\text{L} )</td>
<td>10 ± 7</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Total days of antibiotics</td>
<td>13 ± 1</td>
<td>9 ± 1</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as mean ± SE. APACHE II indicates Acute Physiology and Chronic Health Evaluation II; WBC, white blood cell count. ††P = .01 vs 0 to 12 hours. †P = .05 vs 13 to 24 hours. §Defined as days until temperature lower than 38°C for 24 consecutive hours.
evaluating the treatment of suspected sepsis with a combination of imipenem and cilastatin sodium and with gentamicin sulfate for 72 hours while awaiting culture results did not lead to the emergence of resistant bacteria. Considerable economic advantages may be present if early therapeutic intervention results in similar outcomes but with shorter hospital stays and duration of antibiotic therapy. Cost analysis and further evaluation with larger group sizes should be performed.

Other studies have reported the benefits of early effective therapy on mortality due to bacteremia. Early intervention, however, is stated definitively in only 2 of these studies, and in both studies it is defined as occurring within 24 hours of the onset of bacteremia. Therefore, up to 24 hours was considered an appropriate time interval to initiate antibiotic therapy, a finding supported by our study. Increased mortality associated with infections occurring in patients with increased underlying severity of illness or severity of infection has been demonstrated previously. In our study, increasing APACHE II score was associated with death. The group initially postulated to benefit from timely intervention, ie, those with moderate illness and moderate predicted mortality (APACHE II score, 11-20) did have a lower mortality rate when antibiotics were withheld for 12 to 24 hours. This finding, however, was relatively isolated and would certainly need confirmation before incorporation into patient care protocols.

Our study did not demonstrate a deleterious effect on outcome by withholding therapy before the availability of early culture data. Antimicrobial agents are expensive, with potential toxic effects, and misuse may lead to resistant organisms. Directing therapy based on microbiologic data may decrease inappropriate antibiotic use and limit unnecessary cost and exposure to toxic effects.


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REFERENCES


Discussion

John M. Davis, MD, Neptune, NJ: The authors have prospectively collected and analyzed data from 274 patients who presented with nosocomial infections in an effort to answer the question whether an antibiotic holiday is harmful to the patient. More specifically, does a delay in treatment after a febrile episode result in a higher mortality than empiric therapy with broad-spectrum antibiotics before specific microbiologic data are available? Because this study did not randomize patient treatment options, there is a bias by the treating physician that those patients not on therapy for more than 24 hours were significantly younger than the empirically treated group.

To correct for this bias, did the authors submit their data to a multiple logistic regression analysis with a correction for age? I think that may make their conclusions stronger. It would appear both from the manuscript and the presentation that those younger patients primarily had line infection as witnessed by the gram-positive infection rate and their data shown here. So they are selecting out a much less severely infected group of patients.

Are the authors convinced enough by their data that they would be willing to submit to or undertake a randomized control study, and I reiterate Dr Lipsett’s comments from earlier, a paper by this group, as to what is the next step—How would you go about putting this study together?

What was the policy regarding switching antibiotics in the empirically treated group? In what percent of patients were antibiotics actually switched when the lab came back and indicated that you were not covering the infection that you prophylactically treated group?

And then finally, were the deaths in the study related to septic events or from underlying infections that were not related to antibiotic therapy? Were these infections truly nosocomial? It is hard to tell either from your presentation or the manuscript whether they all followed surgical procedures. Is
it possible that you have some patients here that had an undetected infection that was recognized, really community acquired and recognized after they were in the hospital?

Dr Pelletier: Your first question is regarding whether there may be variables that were not controlled for. Interestingly, patients treated at later intervals tended to have a lower age but similar APACHE II scores. There is a possibility that there is a variable that accounts for increasing severity of illness that is not accounted for in that.

We did look at other factors, including the acute physiology score, which were similar. Other variables that might normally be associated with mortality, such as the presence of being ventilated at the time of diagnosis or hemodialysis, interestingly, are counterintuitive. In one group they had a higher incidence of ventilation and dialysis, but yet, even with delayed therapy, they had a lower mortality. We did try to look for confounding factors. Logistic regression was not performed on this study because in several areas, especially when divided into BSI or pneumonia, the groups were small and would not have had enough power for logistic regression.

I have to admit, I expected to be able to accept the original hypothesis that waiting for microbiologic data would be harmful. The study initially was started after an evaluation of pneumonia in our patient population, and as you saw here, those with minimal and moderate illness had a stepwise increase in mortality, although it did not reach statistical significance. We tried to demonstrate this in a larger group and were surprised by our results.

Developing a randomized study would have multiple confounding factors. It would be difficult to decide on who has pneumonia, which empiric antibiotics would be given, and which patients would be sick enough or be suspicious enough that we would exclude.

As far as the percent of what patients were on appropriate antibiotic therapy empirically and which percent of patients were changed, previous studies have looked at this and have demonstrated that patients who are treated with empiric therapy or not treated at all and then were later found to have incorrect empiric therapy or started on the appropriate therapy at the time of BSI had improved outcome. These data are currently being evaluated and are not available at this time.

Another question regarded mortality. The mortality described here is crude mortality and is not specific for if it was a death due to infection or other underlying illness. We did look at the percentage of patients who died while receiving antibiotic therapy, and their tendencies were similar as presented, and therefore that was not presented in detail.

Your last question addressed if these truly are nosocomial infections. I believe that they were. Patients with minimal illness had an onset from time of admission to fever of a mean of 6 days. That may be a questionable group; however, few differences were found in those groups. Patients with minimal to moderate and severe illness had a mean time from fever to admission of 10 to 20 days, and it would be unlikely that it would be a community-acquired infection.

E. Patchen Dellinger, MD, Seattle, Wash: The title of your paper refers to waiting for microbiology results. The data you present state that antibiotics are given under 12, 12 to 24, or more than 24 hours, with no information given as to whether a culture was done, whether susceptibilities were done, and if so, whether the physicians looked at them or knew the results.

There are papers from quite a few years ago demonstrating that when physicians know the results of cultures done, they tend to prescribe appropriate antibiotics, but that a huge percentage of cultures done are not looked at and inappropriate antibiotics prescribed. So I think your title is a little misleading unless you know in fact that cultures and susceptibilities were done, when they were available, and whether they were looked at.

The other thing is that there is a bias in this study that you will never be able to escape no matter how often you reanalyze it, and that is that patients given antibiotics within 12 hours are simply not the same as patients given antibiotics 75 hours later regardless of what the APACHE II score is. When somebody is really worried about a patient, they give antibiotics right away and they will not wait to make sure of their diagnosis. Now, whether the patient is infected or not, we don’t know, but they are not the same patients.

Dr Pelletier: The availability of microbiologic results is being investigated at this time. When we reviewed the results, we were surprised to see the remarkable difference in the time that patients were treated and the little standard error that was present. The means were approximately 6 hours, 24 hours, and more than 2 days. That is where we decided that microbiologic data would most likely be present and hopefully interpreted.

You suggest patients who are treated earlier are different from those treated later. I would have to agree with you. Our findings were somewhat interesting. We found that patients who had fever during the early time of their admission tended to be treated earlier than patients who had been in the ICU or had been in the hospital from longer times. We thought that this may reflect an understanding of the disease process that was going on. A patient during their early admission may have some-what of an unknown diagnosis. Fever in that patient may prompt treatment earlier, as opposed to someone who is in the ICU who has multiple lines and other more likely causes of infection that may be known. Patients may be willing to wait for microbiologic data to direct appropriate therapy.

Basil A. Pruitt, MD, San Antonio, Tex: I have some concern about the fact that in both the mid-range and the high-range severity scores, the cultures or findings were heavily weighted to gram-positive infections, and we discussed yesterday that there may be little, if any, comorbidity associated with that. So have you sorted the patients based on the causative organism as gram-negative Candida vs gram-positive?

Secondly, have you sorted on the basis of hypotensive or hyperdynamic shock, which might make a difference?

And lastly, is the logical extension of this study no antibiotic treatment at all?

Dr Pelletier: Please let me start with the last question first. The contention of this presentation is not that antibiotic therapy kills people. However, what this study does contend is not all fevers require immediate therapy. Also, there may be other factors involved for the survival of a patient other than early and appropriate antimicrobial therapy. In our study, we have looked at over 1500 patients, and APACHE II score was the strongest single independent predictor of mortality. Maybe underlying severity of illness is a stronger predictor.

We did not evaluate or control for the presence of shock. Patients with moderate or severe illness did tend to have a higher degree of gram-positive organisms in this paper. Mortality was not different when we evaluated for gram-negative or gram-positive infection, although I must add that the groups were somewhat small.

David Spain, MD, Louisville, Ky: I have just one question. Did you define each infection prospectively? That is, do you have specific diagnostic criteria for pneumonia? How do you counter the argument that what happened was you may have been treating patients with colonization without a documented or diagnosable infection?

Dr Pelletier: All the patients discussed here had documented infection. We defined documented infection as culture of a predominant organism from a normally sterile site that prompted treatment. For pneumonia, it required the presence of a predominant organism in sputum; the presence of systemic symptoms, such as a white blood count and fever; radiographic evidence of a newer or changing infiltrate. Blood stream infection was defined as the presence of a positive culture, except for S epidermidis, which required 2 positive cultures.