Risk Factors for Hospital-Acquired Staphylococcus aureus Bacteremia

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Background: Staphylococcus aureus bacteremia (SAB) acquired in hospitals continues to be a frequent and serious complication to hospitalization, and no previous case-control studies dealing with risk factors of this severe disease are available.

Methods: Based on a 1-year prospective analysis, the data from all patients with hospital-acquired SAB admitted to 4 hospitals in Copenhagen County, Denmark, from May 1, 1994, through April 30, 1995, were evaluated. Eighty-five patients with hospital-acquired SAB were matched to 85 control patients with a similar primary diagnosis at admission (matched controls). Of these, 62 patients with hospital-acquired SAB were compared with 118 other patients with a similar time of admission, who were randomly selected with no clinical evidence of SAB (unmatched controls).

Results: The incidence of hospital-acquired SAB was 0.71 per 1000 hospital admissions. The presence of a central venous catheter (odds ratio, 6.9; 95% confidence interval [CI], 2.8-17.0), anemia (odds ratio, 3.3; 95% CI, 1.4-7.6), and hyponatremia (odds ratio, 3.3; 95% CI, 1.5-7.0) was significantly associated with hospital-acquired SAB in a conditional and a usual logistic regression analysis. Nasal carriage was not an independent risk factor, but nasal carriers among patients in surgery (odds ratio, 4.0; 95% CI, 1.3-13.0) had a significantly higher risk for hospital-acquired SAB compared with matched and unmatched controls. The presence of hospital-acquired SAB increased the mortality rate 2.4-fold (95% CI, 1.1-5.2).

Conclusions: The presence of a central venous catheter is an important risk factor, and hyponatremia and anemia are associated with the development of hospital-acquired SAB. Furthermore, hospital-acquired SAB in itself increases mortality.

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hospital in Copenhagen County and 0.30 per 1000 inhabitants per year. No cases were clustered in either time or location within the hospitals.

MATCHING

Cases are compared with the 85 matched controls in Table 1. Primary diagnoses at admission were most often cancer, nephrological diseases, and arteriosclerotic diseases.

RISK FACTORS

The time since admission to the hospital was longer for cases (median, 25 vs 5 days) (Table 3) and the patients were younger (median, 61 vs 70 years) compared with matched controls. Also, the total length of stay was longer for cases than matched controls (median, 24 vs 13 days). Cases and matched controls are compared in univariate and multivariate analysis in Table 3. The presence of a CVC, anemia, hyponatremia, and blood transfusion was significantly associated with hospital-acquired SAB in the univariate analysis, while surgery, corticosteroid treatment, immunosuppressive disease, nasal carriage, sex, age, use of antibiotics, and presence of a PVC did not increase the risk for hospital-acquired SAB. The risk of SAB highly correlated with the severity of hyponatremia and anemia (data not shown).

VARIABLE ASSOCIATIONS

Only the presence of a CVC, anemia, and hyponatremia was directly connected to hospital-acquired SAB as judged by the independence graph (Figure 1). In
For unmatched controls, the following variables were registered: primary diagnosis, age, sex, nasal carriage, surgery, presence of a CVC and/or a PVC, hemodialysis, and use of antibiotics.

Three months after the visit, the medical records of cases and control patients were examined (reviewed). From this, time from visit to review (effective observation time) (maximal, 90 days), discharge, or death was registered. Basic demographic data were obtained from registration documents and noted for each patient, and matching and registration were performed by the same person (A.G.J.). To be sure that the patient had not died at home, information about outcome was confirmed using a central data register.

**MICROBIOLOGIC METHODS**

All specimens were routinely registered in a microbiologic database system (ADBakt, Autonik AB; Ramsta, Skoldinge, Sweden) running on a digital minicomputer (model VAX 4200; Compaq Computer Corp, Houston, Tex) with 40 terminals connected.44 The blood culture system used was Colorbact (Statens Serum Institut, Copenhagen).45,46 All S aureus strain isolates were phage typed according to the method of Blair and Williams47 using the international set of typing phages. The phages were used in concentrations of routine dilution: 100 and 1000 times the routine dilution. The subdivision into phage groups and complexes was done according to Parker.48

**STATISTICAL METHODS**

All potential risk factors were dichotomized. Unmatched controls were compared with patients with SAB only in univariate analysis, while matched controls were compared with patients with SAB in a multivariate analysis. For the latter group, factors statistically associated with SAB in univariate analysis, as well as factors considered of importance from the English-language literature, were included. Associations between this selection of variables were investigated in a chain independence graph or chain graph.49-52 Based on the analysis of all possible 2- and 3-way tables and using a 1% level of significance, associations between variables are illustrated in Figure 1. Variables are grouped in 3 time levels (or causality levels) surrounded by a box. Variables on the same level are considered to be risk factors on an equal footing for hospital-acquired SAB. Variables on level 1 are underlying factors (age, sex, and immunosuppressive condition). Variables on level 2 are hospital-related factors (surgery, blood transfusion, and CVC). Level 3 contains the response variable (hospital-acquired SAB). Some variables are connected by lines (eg, hyponatremia and anemia). Each line indicates a dependent relationship of the connected variables given the set of all variables on the same or earlier levels. If 2 variables (eg, hyponatremia and blood transfusion) are on different levels, the line is equipped with an arrowhead. Thus, arrows might be regarded as causal links, while lines indicate unspecified associations. Variables directly associated with hospital-acquired SAB in the chain graph (CVC, anemia, and hyponatremia) (Figure 1) were chosen as covariates in the logistic regression analysis (Table 3). Both conditional (matched) logistic regression and usual (unmatched) logistic regression were performed. Statistical analysis was performed with computer software (SAS/STAT; SAS Institute Inc, Cary, NC).

The duration of a possible SAB-related mortality effect was tentatively fixed to 10 days following a positive blood culture result. To achieve a reasonable estimate of baseline mortality, matched controls were included in a survival study with hospital-acquired SAB as time dependent and relevant level 1 factors as fixed covariates. Each fixed factor defines 2 groups of patients, and in each of these, a rough mortality rate is given by the number of deaths in that group divided by the total person-time observed (from sampling until discharge or follow-up). If the ratio of these 2 rates was larger than 2, the factor was included in a Cox regression model. This model illustrates the effect on mortality of a covariate (ie, cancer) given by the ratio of cancer and noncancer death intensities (mortality rate ratio). The mortality rate ratio is considered constant in contrast to death intensities, which are time dependent. Kaplan-Meier survival curve estimates were calculated for cases, matched controls, and unmatched controls. Cox regression analysis and Kaplan-Meier estimates reflect the effective observation time; however, the duration of hospital-acquired SAB is only included in the Cox regression analysis.

Addition, the following correlations were demonstrated: blood transfusion correlated positively with the presence of CVC, hyponatremia, and the use of antibiotics; corticosteroid treatment correlated positively with the presence of CVC, immunosuppressive disease, and female sex; surgery correlated positively with the use of antibiotics and male sex; and anemia correlated positively with hyponatremia (Figure 1).

Patients older than 60 years did not have a higher risk for hospital-acquired SAB compared with other patients, using univariate analysis (data not shown), a finding that remained in the independence graph (Figure 1).

The final models of conditional and usual logistic regression analyses are also shown in Table 3. The models revealed that the presence of a CVC remained an independent risk factor and that anemia and hyponatremia were statistically associated in the development of hospital-acquired SAB in both analyses.

**PATIENTS WITH HOSPITAL-ACQUIRED SAB VS OTHER HOSPITALIZED PATIENTS**

Patients with hospital-acquired SAB were compared with a group of other hospitalized patients without SAB (unmatched controls) according to age, time in the hospital, sex, mortality, and primary diagnosis at admission (Table 2). Patients with hospital-acquired SAB were younger (median, 64 vs 73 years), but the mortality and the total number of patients with severe manifestation of disease, such as cancer and severe hematologic disease, were higher among patients with hospital-acquired SAB compared with unmatched controls (Table 2). Arteriosclerotic and gastrointestinal tract diseases were
less frequent and urinary tract disease was more often seen among patients with hospital-acquired SAB compared with unmatched controls (Table 2).

NASAL CARRIAGE AND SURGERY

Nasal carriage was not an independent risk factor for hospital-acquired SAB in a univariate analysis (Table 3). However, nasal culture had been performed in only 61 (72%) of 85 hospital-acquired SAB cases. Univariate analyses focusing on nasal carriage in relation to surgery, intravenous catheters, hemodialysis, and use of antibiotics, including matched and unmatched controls, are presented in Table 4. The table shows nasal carriers among patients in surgery and patients with an inserted CVC had a significantly higher risk for hospital-acquired SAB compared with matched controls and unmatched controls. The risk for hospital-acquired SAB was not significantly influenced by nasal carriage in combination with the presence of a PVC, hemodialysis, or use of antibiotics (Table 4). Matched controls were compared with other hospitalized patients according to all common variables (data not shown). Nephrological disease and immunosuppressive conditions such as corticosteroid treatment were more often registered among matched controls, while arteriosclerotic and gastrointestinal tract diseases were less often seen compared with the group of other hospitalized patients.

MORTALITY

Kaplan-Meier plots of survival curves for patients with hospital-acquired SAB, matched controls, and unmatched controls are presented in Figure 2. The survival curve for patients with hospital-acquired SAB was similar to that for matched controls but significantly lower (P < .01) compared with unmatched controls. Mortality rate ratios regarding age older than 60 years, hospital-acquired SAB, and cancer were calculated. The presence of hospital-acquired SAB (95% confidence interval, 1.1-5.2; P < .05) and age older than 60 years (95% confidence interval, 1.1-5.4; P < .05) increased the mortality 2.4-fold. The mortality rate ratio for cancer was 1.7 (95% confidence interval, 0.8-3.5). However, this was not statistically significant (P = .14) compared with baseline mortality.
Table 3. Univariate and Regression Analyses of Hospital-Acquired SAB Cases and Matched Controls*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases†</th>
<th>Matched Controls†</th>
<th>Univariate</th>
<th>Usual Logistic Regression</th>
<th>Conditional Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from admission, median (range), d</td>
<td>25 (3-189)‡</td>
<td>5 (1-37)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>61 (1-92)§</td>
<td>70 (1-60)</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>CVC</td>
<td>34/84 (40)</td>
<td>8/85 (9)</td>
<td>6.4 (2.8-15.0)§</td>
<td>6.9 (2.8-17.0)‡</td>
<td>10.0 (2.7-37.0)¶</td>
</tr>
<tr>
<td>Anemia</td>
<td>73/85 (86)</td>
<td>52/85 (61)</td>
<td>3.9 (1.8-8.2) †</td>
<td>3.3 (1.4-7.6)‡</td>
<td>4.5 (1.6-13.0)¶</td>
</tr>
<tr>
<td>Hypotension</td>
<td>38/85 (45)</td>
<td>16/85 (19)</td>
<td>3.5 (1.8-7.0) ‡</td>
<td>3.3 (1.5-7.0)‡</td>
<td>3.2 (1.2-8.1)¶</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>45/84 (54)</td>
<td>26/85 (31)</td>
<td>2.6 (1.4-5.0) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>Surgery</td>
<td>35/85 (41)</td>
<td>26/85 (31)</td>
<td>1.6 (0.9-3.0) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>44/85 (52)</td>
<td>38/85 (45)</td>
<td>1.3 (0.7-2.4) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>Immunosuppressive disease</td>
<td>45/85 (53)</td>
<td>41/85 (48)</td>
<td>1.2 (0.7-2.2) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>Nasal carriage</td>
<td>13/61 (21)</td>
<td>16/78 (21)</td>
<td>1.1 (0.5-2.4) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>Male sex</td>
<td>44/85 (52)</td>
<td>47/85 (55)</td>
<td>0.9 (0.5-1.6) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>Age &gt;60 y</td>
<td>43/85 (51)</td>
<td>48/85 (56)</td>
<td>0.8 (0.4-1.4) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>Use of antibiotics</td>
<td>14/85 (16)</td>
<td>18/85 (21)</td>
<td>0.7 (0.3-1.6) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
<tr>
<td>PVC</td>
<td>28/85 (33)</td>
<td>37/85 (44)</td>
<td>0.6 (0.3-1.2) §</td>
<td>Ni</td>
<td>Ni</td>
</tr>
</tbody>
</table>

* SAB indicates Staphylococcus aureus bacteremia; OR, odds ratio; CI, confidence interval; CVC, central venous catheter; Ni, not included in the final regression model; PVC, peripheral venous catheter; and ellipses, data are not applicable.
† Data are given as the number/total (percentage), unless otherwise specified.
‡ Younger (P < .05) compared with matched controls.
§ Older (P < .01) compared with matched controls.
¶ P < .01.
** P < .05.

Table 4. Univariate Analysis of Nasal Carriage of Hospital-Acquired SAB Cases and Matched and Unmatched Controls*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases†</th>
<th>Matched Controls†</th>
<th>OR (95% CI)</th>
<th>Cases†</th>
<th>Unmatched Controls†</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal carriage plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>8/69 (12)</td>
<td>1/81 (1)‡</td>
<td>10.5 (1.3-85.3)‡</td>
<td>8/52 (15)</td>
<td>5/116 (4)§</td>
<td>4.0 (1.3-13.0)‡</td>
</tr>
<tr>
<td>CVC</td>
<td>6/69 (9)</td>
<td>1/78 (1)§</td>
<td>7.3 (0.9-62.5)§</td>
<td>6/50 (12)</td>
<td>1/118 (1)‡</td>
<td>16.0 (1.9-136.2)‡</td>
</tr>
<tr>
<td>PVC</td>
<td>5/72 (7)</td>
<td>5/81 (6)</td>
<td>1.1 (0.3-4.7)</td>
<td>5/55 (9)</td>
<td>13/118 (11)</td>
<td>0.6 (0.2-2.0)</td>
</tr>
<tr>
<td>Intravenous catheter</td>
<td>11/82 (13)</td>
<td>6/82 (7)</td>
<td>2.0 (0.7-5.6)</td>
<td>11/60 (18)</td>
<td>14/118 (12)</td>
<td>1.7 (0.7-3.9)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>3/66 (5)</td>
<td>2/79 (3)</td>
<td>1.8 (0.3-11.3)</td>
<td>3/45 (7)</td>
<td>1/117 (1)</td>
<td>8.3 (0.8-81.7)</td>
</tr>
<tr>
<td>Use of antibiotics</td>
<td>4/65 (6)</td>
<td>2/79 (3)</td>
<td>2.5 (0.5-14.2)</td>
<td>4/48 (8)</td>
<td>6/117 (5)</td>
<td>1.7 (0.5-6.3)</td>
</tr>
</tbody>
</table>

* SAB indicates Staphylococcus aureus bacteremia; OR, odds ratio; CI, confidence interval; CVC, central venous catheter; and PVC, peripheral venous catheter.
† Data are given as the number/total (percentage).
‡ P < .01.
§ P < .05.

from larger tertiary hospitals or referral centers in the United States. The incidence rate for hospital-acquired SAB was relatively high (0.71 per 1000 admitted patients), indicating that S aureus is a major pathogen in infections acquired by hospitalized patients.

Matching was well performed concerning the grouping of primary diagnosis at admission, as all pairs except one belonged to the same diagnostic group (Table 1). The time from admission to visit was longer for patients with SAB compared with matched controls (Table 3). This is in accordance with a study by Duggan et al; however, they have demonstrated that risk of infection is relatively constant depending on preconditions and hospital-related treatments rather than time in the hospital. Matching on Acute Physiology and Chronic Health Evaluation III score and time since admission would have been ideal in the present study, and the mortality risk for these groups may be influenced by these factors. Observations required for Acute Physiology and Chronic Health Evaluation scoring were not possible to obtain in the study.

However, a recent study by Yzerman et al did not find a clear correlation between the prebacteremic health status (Acute Physiology and Chronic Health Evaluation II) and risk of dying as a consequence of nosocomial SAB. The longer median time since admission for cases compared with matched controls may suggest differences in the severity of illness. The reason for this may be the relatively long time required in the acquisition of hospitalized SAB and the relatively few controls available because the selection was carried out immediately after the patient with SAB was visited. Patients with SAB were younger compared with matched controls (Table 3). It is, therefore, not likely that older age, per se, is an important risk factor for the development of hospital-acquired SAB. The longer total length of hospital stay for cases compared with controls may be due to SAB, and not necessarily differences in underlying conditions.

Factors statistically associated with hospital-acquired SAB in the univariate analysis (Table 3) were anemia, hyponatremia, blood transfusion, and presence
Several other risk factors have previously been shown to be of importance for hospital-acquired SAB, including sex, recent surgery, the presence of a PVC, immunosuppressive conditions such as cancer, diabetes mellitus, and alcohol abuse. However, none of these individual factors proved to be independent risk factors for hospital-acquired SAB in our study. One recent study of hospital-acquired septicemia has shown that these 2 variables are independently protective, while another study of nosocomial bacteremia due to methicillin-resistant S aureus has demonstrated that patients who have received prior antibiotic therapy have a significantly increased risk of infection. Nasal carriage of S aureus was not included in the independence graph model in the present study, as a nasal culture had been obtained from only 139 cases and controls. However, nasal carriage included in a regression analysis showed an odds ratio of 6.0 (95% confidence interval, 0.66-54.0) (P = .10). Previous studies have indicated that it is an important risk factor for infection and serves as a source from which the organism can be spread to others; eradication of nasal carriage using intranasal mupirocin calcium ointment has been useful in several studies. However, this has also led to the emergence of mupirocin resistance and identification of populations at continuing risk is, therefore, needed to limit the use of mupirocin. Nasal carriers in surgery and nasal carriers with a CVC had a higher risk for hospital-acquired SAB in univariate analyses including matched and unmatched controls (Table 4). Unfortunately, data were not sufficient for further evaluation in a multivariate model.

Hemodialysis has been connected to SAB in several studies as patients undergoing hemodialysis often are carriers of S aureus. In the present study, hemodialysis was frequently related to primary diagnosis, which was used as a matching variable and was, therefore, not evaluated in the multivariate model. However, nasal carriers undergoing hemodialysis had a higher risk compared with other patients, but this finding was not significant (P = .66) (Table 4).

For many years, SAB has been associated with high mortality. The mortality of patients with SAB was higher (Table 2 and Figure 2) compared with unmatched controls but not compared with matched controls (Figure 2), although patients with SAB were younger (Tables 2 and 3). To evaluate if this is true, the Cox regression model was performed, and the results demonstrated that hospital-acquired SAB in itself and age (>60 years) increase the mortality independently, similar to the findings by Julander. The finding that hospital-acquired SAB is independently involved is in contrast to the same mortality rates seen for cases and matched controls in Figure 2. This may be due to the possible SAB-related mortality effect following a positive blood culture result included in the regression analysis. Antibiotic treatment was not specifically considered in this study; however, the recommendations...
for these patients were the same for all patients during the study period. A group of unmatched controls was included to investigate if other factors may be important. This group emphasizes findings similar to the matched controls and provides important information about outcome.

In conclusion, hospital-acquired SAB continues to be a frequent and serious complication to hospitalization. Furthermore, this study may indicate that hypotension and anemia are 2 factors that should be focused on in future studies.

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