Quantifying the Relationship between *Staphylococcus aureus* Bacteremia and *S. aureus* Bacteriuria: A Retrospective Analysis in a Tertiary Care Hospital

Miquel B. Ekkelenkamp, Jan Verhoef, and Marc J. Bonten

University Medical Center Utrecht, Department of Medical Microbiology, Utrecht, The Netherlands

In this retrospective cohort study, patients who had *Staphylococcus aureus* bacteremia but who lacked signs and symptoms of urinary tract infection due to *S. aureus* and who did not have an indwelling urinary catheter had a likelihood of *S. aureus* bacteriuria of 2.5% (2 of 79 patients). Therefore, we strongly question the theory that *S. aureus* bacteremia causes *S. aureus* bacteriuria.

It is popularly believed that *Staphylococcus aureus* bacteremia causes *S. aureus* bacteriuria, especially in the case of endocarditis [1–3]. On the basis of this assumption, it is often advised to seek a distant site of infection as a source of (transient) bacteremia in the case of *S. aureus* bacteriuria. However, data that confirm this widely assumed association are scarce, and among 39 patients with *S. aureus* bacteriuria but without demonstrated bacteremia, a distant site of *S. aureus* infection was demonstrated in only 1 patient [4]. Moreover, in the most frequently cited study in this regard [5], an association between *S. aureus* bacteremia and *S. aureus* bacteriuria was reported, but causality was not claimed. In fact, it was concluded that “staphyloccocal bacteriuria appears to be a frequent and unexplained concomitant of *S. aureus* bacteremia” (p. 306).

If the theory that *S. aureus* bacteriuria is a reflection of bacteremia is not true, adherence to it may lead to extensive and unnecessary “source investigations” in patients with *S. aureus* bacteriuria and to disregarding the urinary tract as a focus of *S. aureus* bacteremia. *S. aureus* is, however, known to cause urinary tract infection (UTI), which may well be the source of *S. aureus* sepsis syndrome [6]. Furthermore, it has been demonstrated that urinary catheters predispose to urinary colonization with *S. aureus* [6–8] and that colonization with this microorganism is a risk factor for subsequent infection [6, 9].

In this study, we aimed to quantify the relationship between *S. aureus* bacteremia and *S. aureus* bacteriuria. We hypothesized that, if *S. aureus* bacteremia truly causes *S. aureus* bacteriuria, we should observe this phenomenon in patients without UTI and without risk factors for urinary colonization with *S. aureus* (specifically, the presence of urinary catheters), because only such could, in our opinion, be unambiguously attributed to *S. aureus* bacteremia.

**Methods.** Patients who received a diagnosis of documented *S. aureus* bacteremia during the period from 1 June 2001 to 1 June 2006 were identified in the database of the bacteriology department of the University Medical Center Utrecht (a tertiary care hospital in Utrecht, The Netherlands, with 1024 beds). From these patients, 2 groups were selected: patients who had a urine sample obtained for culture on the same day as a positive result of blood culture result (group 1), and patients who had *S. aureus* bacteriuria on any other day during this 5-year period (group 2), with an isolate with a similar susceptibility pattern (difference in susceptibility of *≤*1 antibiotic between the urine and blood isolates). Patients with a clinical diagnosis of *S. aureus* UTI were excluded from groups 1 and 2 and analyzed separately, because in these cases, the bacteriuria was regarded as the cause of *S. aureus* bacteremia rather than its effect.

For each patient, we recorded the age, the number of positive results of blood culture bottles in a window period of 2 days before until 2 days after obtaining urine for culture, results of urine cultures, and presence of an intravesical catheter. The definite source of *S. aureus* bacteremia was established on the basis of patient charts. In patients with a clinical diagnosis of endocarditis, we evaluated whether the case complied with the Duke criteria [10].

The diagnosis “obvious UTI” was defined by the following criteria (all 5 criteria had to be met): (1) UTI diagnosed by the clinician, (2) presence of leukocyturia, (3) no other probable focus of bacteremia, (4) presence of *S. aureus* bacteriuria (difference in susceptibility of *≤*1 antibiotic between urine and blood isolate), and (5) presence of either localizing symptoms, a recent surgical procedure or manipulation in the urinary tract, or urinary obstruction. The medical charts of these patients
Table 1. Relationship between *Staphylococcus aureus* bacteriuria, *S. aureus* bacteremia, and urinary tract infection in different studies.

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>No. of patients with <em>S. aureus</em> bacteriuria</th>
<th>Percentage of bacteriuric patients</th>
<th><em>S. aureus</em> bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demuth et al. [8] (1979)</td>
<td>127</td>
<td>73&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15</td>
</tr>
<tr>
<td>Muder et al. [6] (2006)</td>
<td>102</td>
<td>82</td>
<td>13–21&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Present report</td>
<td>470</td>
<td>64</td>
<td>9.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> These patients were defined as having undergone a “recent urinary catheterization or invasive procedure.”

<sup>b</sup> The 21% value includes patients with late-occurring *S. aureus* bacteremia (i.e., bacteremia that occurred >1 week after original urine culture).

were examined for previous invasive urologic procedures and for urologic neoplasms.

Blood cultures were incubated for a minimum of 5 days at 35°C in an automated detection system. Urine specimens were processed with a dip slide (Uricult; Orion Diagnostics), and, when the results were positive (≥10<sup>4</sup> cfu/mL), they were subcultured onto blood agar. Identification and susceptibility testing were performed using an automated system and software; the identification was confirmed by testing free and bound coagulase.

The associations between *S. aureus* bacteriuria and the presumed risk factors were tested for statistical significance by $\chi^2$ analysis and $\chi^2$ analysis for trend, using SPSS software, version 12.0 (SPSS).

**Results.** In the studied 5-year period, a total of 64,256 urine samples were processed at our laboratory. Of the 16,667 samples with positive urine culture results, 8928 were midstream urine samples, and 7739 were catheter-obtained samples. Six hundred eighty-five urine cultures (4.1% of all positive culture results) yielded *S. aureus*; 222 were midstream urine cultures (2.5% of all midstream urine cultures with positive results), and 463 were catheter cultures (6.0% of all catheter cultures with positive results); samples were obtained from 470 patients (167 patients for midstream urine samples and 303 patients for catheter-obtained samples). During this period, 42,101 sets of blood samples for culture were obtained, of which 5519 yielded positive results, and 950 yielded *S. aureus*, from 515 patients.

In the total group of patients with *S. aureus* bacteriuria (n = 470), 64% had urinary catheters in place, and 9.6% had *S. aureus* bacteremia. This confirms previous observations that intravesical catheters are an important risk factor for *S. aureus* bacteriuria (table 1).

In group 1 (table 2), 153 patients had urine culture samples obtained on the same day that *S. aureus* bacteremia was detected and did not have a diagnosis of UTI; of these culture samples, 79 were midstream urine samples, and 74 were catheter-obtained urine samples. Twelve patients (7.8%) had *S. aureus* bacteriuria; 10 of these patients had intravesical catheters. The likelihood of *S. aureus* bacteriuria in the case of *S. aureus* bacteremia and in the absence of a catheter was, therefore, 2.5% (2 of 79 patients). Of note, in 1 of these 2 patients (a patient undergoing hemodialysis who had oliguria and renal failure associated with glomerulonephritis), it was questionable

<table>
<thead>
<tr>
<th>Focus of bacteremia</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>11 (8)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Intravascular catheter infection</td>
<td>39 (28)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Phlebitis/infected endovascular prosthesis</td>
<td>19 (13)</td>
<td>...</td>
</tr>
<tr>
<td>Skin/wound infection</td>
<td>9 (6)</td>
<td>...</td>
</tr>
<tr>
<td>Abscess</td>
<td>12 (9)</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
<td>21 (15)</td>
<td>3 (25)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (21)</td>
<td>4 (33)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**NOTE.** Groups are defined in Methods.

<sup>a</sup> Diagnoses for these 3 patients were osteomyelitis, spondylodiskitis, and upper respiratory tract infection.

<sup>b</sup> Of the 4 patients with no clinically identified focus for the *Staphylococcus aureus* bacteremia, 1 complied with criteria 2–5 for urinary tract infection.

<sup>c</sup> Of the 11 patients with no clinically identified focus for the *S. aureus* bacteremia, 6 complied with criteria 2–5 for urinary tract infection.
whether S. aureus bacteriuria could be attributed to S. aureus bacteremia.

The only independent risk factor for S. aureus bacteriuria among patients with S. aureus bacteremia was the presence of indwelling urinary catheters (OR, 6.0; 95% CI, 1.1–41.4). We found no association of S. aureus bacteriuria with age, endocarditis, or number of positive blood culture results.

In group 2 (table 2), 23 patients had S. aureus bacteremia and S. aureus bacteriuria on different days. Eighteen patients (78%) had urinary catheters in place. In 13 patients, documented S. aureus bacteriuria preceded S. aureus bacteremia (median interval, 5 days; range, 1–140 days), and in 10 patients, S. aureus bacteremia preceded S. aureus bacteriuria (median interval, 19 days; range, 1–162 days).

Five patients in group 2 did not have urinary catheters in place. Of these patients, 1 had severe kidney disease (acute rejection of a kidney transplant) and was oliguric; in 2 patients, the urine culture results became positive >3 months after S. aureus bacteremia; and in 1 patient, bacteriuria (which occurred 5 days before S. aureus bacteremia and sepsis syndrome) may have indicated UTI. This leaves only 1 patient without an identified focus for S. aureus bacteriuria in which “unexplained” S. aureus bacteriuria might have been attributable to the bacteremia.

Sixteen (31%) of the 51 patients with S. aureus bacteremia and S. aureus bacteriuria fulfilled the criteria for diagnosis of S. aureus UTI. Twelve of these patients (75%) had urinary catheters in place, 12 (75%) had previously undergone invasive urologic procedures (such as changing of a nephrostomy catheter, placement of a suprapubic urine catheter, radical cystectomy, transurethral resection of the prostate, and renal transplantation), and 8 (50%) had been given a diagnosis of urologic neoplasms.

Seven of the 46 patients with S. aureus bacteremia with an “unknown origin” fulfilled criteria 2–5 for UTI but lacked the treating physician’s diagnosis to be qualified as such. Pyuria and bacteriuria were demonstrated in the week previous to the treating physician’s diagnosis to be qualified as such. Pyuria and bacteriuria identified in a midstream urine specimen on separate days. We identified 7 patients who fulfilled all of the criteria for UTI except for criterion 1 (i.e., diagnosis made by the treating clinician). One may speculate that this finding suggests that S. aureus UTI was underdiagnosed as a cause of S. aureus bacteremia.

Because of its retrospective nature, this study has several limitations. Urine samples were not obtained in a protocized manner, and we could analyze the diagnostic samples only as ordered by the treating physicians; this probably biased our observations toward a higher percentage of patients with UTI. Furthermore, it cannot be excluded that blood samples were obtained for culture first and that urine samples were obtained after antibiotic therapy had been started, therefore yielding false-negative results. Yet all of the previous studies also had this limitation—and probably to a larger extent, because wider intervals (up to 48 h) were accepted. Finally, only the diagnoses of UTI and endocarditis were confirmed on the basis of predetermined criteria.

In short, on the basis of the results of this study—and the evidence in literature—we refute the widely held belief that S. aureus bacteriuria is a common effect of S. aureus bacteremia and that S. aureus bacteriuria in itself justifies extensive source investigations. A prospective study is, however, required to provide a definitive answer to this question.

Acknowledgments

Potential conflicts of interest. J.V. has served as a consultant for Aventis and Roche Pharmaceuticals. M.J.B. has received recent research funding from 3M, has served as a consultant for Aventis, and is on the Speakers’ Bureau for 3M, Pfizer, and Chiron. M.B.E.: no conflicts.

References