Evaluation of *Staphylococcus aureus* Bacteriuria Patients in Three-Year Period in an Oncology Hospital

Bir Onkoloji Hastanesinde Üç Yıllık Periyoddaki *Staphylococcus aureus* Bakteriüri Hastalarının Değerlendirilmesi

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ABSTRACT

Introduction: *Staphylococcus aureus* bacteriuria (SABU) is encountered in patients with long-term care, urological abnormalities, older age, and comorbidities. SABU may be caused by contamination, colonization, asymptomatic bacteriuria, urinary tract infection (UTI), or invasive disease, its clinical relevance and therapy unclear. This study evaluated individuals with *S. aureus* isolated in urine cultures in an oncology hospital.
Materials and Methods: 82 patients with *S. aureus* urine isolation were studied retrospectively. Age, gender, clinical data and laboratory reports were evaluated. Concurrent *S. aureus* bacteremia (SAB) development was also determined.
Results: 52% of the patients were male and 48% were female. Overall, 63.4% of the patients had cancer. Among these, 39.02% had genitourinary cancer, 8.53% had gastrointestinal cancer, 6.09% had breast cancer, 2.43% had respiratory tract cancer, 2.43% had lymphoma, 1.21% had acute myeloid leukemia, and 3.65% had other cancers (brain, bone, and soft tissue). 68.2% of the patients had urological abnormalities, and 18.2% had urinary catheters. 39.02% of *S. aureus* were resistant to methicillin. In SABU patients' average level of CRP was 62.17mg/L and procalcitonin was 0.3656ng/ml. Five of the SABU patients (6.09%) had simultaneous *S. aureus* in their blood cultures, and all of it was secondary to bacteriuria and seeding following urological instrumentation/catheterization.
Conclusion: The urological abnormalities/cancers and urinary catheter use were significant underlying factors in SABU in patients. The differential diagnosis of SABU should be based on clinical/laboratory data and presence of pyuria. For avoiding unnecessary antibiotic use, repeated urine and blood cultures may be useful in guiding clinicians for SABU patients.

Keywords: *Staphylococcus aureus*, bacteriuria, methicillin resistance

ÖZET

Amaç: *Staphylococcus aureus* bakteriürisine (SABU) uzun süreli bakım alan, ürolojik anormallikleri olan, ileri yaştaki ve komorbiditeleri olan hastalarda rastlanmaktadır. SABU, kontaminasyon, kolonizasyon, asemptomatik bakteriüri, idrar yolu enfeksiyonu (İYE) veya invaziv hastalık gibi sebeblerle oluşabileceği için klinik önemi ve tedavisi belirsiz olarak kalmış bir durumdur. Bu çalışmada, bir onkoloji hastanesinde idrar kültürlerinde *S. aureus* izole edilen hastalar değerlendirilmiştir.
Gereç ve Yöntemler: İdrar kültürlerinde *S. aureus* izolasyonu yapılan 82 hasta çalışmaya alınmıştır. Yaş, cinsiyet, klinik veriler ve laboratuvar raporları değerlendirilmiştir. Eş zamanlı *S. aureus* bakteriyemisi (SAB) gelişimi de araştırılmıştır
Bulgular: Hastaların %52'si erkek, %48'i kadındı ve hastaların %63,4'ü kanser hastasıydı. Hastaların %39,02'sinde genitoüriner, %8,53'ünde mide-bağırsak, %6,09'unda meme, %2,43'ünde solunum sistemi kanseri, %2,43'ünde lenfoma, %1,21'inde akut miyeloid lösemi ve %3,65'inde diğer kanserler (beyin, kemik, yumuşak doku) bulunmaktaydı. Hastaların %68,2'sinde ürolojik anormallik, %18,2'sinde de

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idrar sondası kullanımı vardı. *S. aureus'da* metisiline direnci %39,02'idi. SABU hastalarında ortalama CRP düzeyi 62,17 mg/L iken, prokalsitonin düzeyi 0,3656 ng/ml olarak saptandı. Beş (%6,09) SABU hastasında kan kültürlerinde de eş zamanlı olarak *S. aureus* üremesi vardı ve bunların tamamı bakteriüri ve ürolojik enstrümantasyon/kateterizasyon sonrası idrar yollarından yayılıma sekonder olarak ortaya çıkmıştı.

Sonuç: SABU'nun oluşmasında altta yatan önemli faktörler arasında ürolojik anormallikler/kanserler ve idrar sondası kullanımı yer almaktadır. SABU'nun ayırıcı tanısı klinik/laboratuvar verilerine ve piyüri varlığına dayanarak yapılabilir. Gereksiz antibiyotik kullanımını önlemek amacıyla SABU hastalarında tekrarlayan idrar ve kan kültürlerinin alınması klinisyene tanıda yol gösterici olacaktır.

Anahtar Kelimeler: *Staphylococcus aureus*, bakteriüri, metisilin direnci

Introduction

Staphylococcus aureus infections are a significant cause of mortality and morbidity in immunosuppressive patients. *S. aureus* is present in about 20-30% of the nose and skin of healthy adults. For hospitalized patients and hospital staff, these percentages are higher. *S. aureus* infections range from mild to life-threatening infections including skin infections, abscesses, bacteremia, endocarditis, osteomyelitis, and pneumoniae. *S. aureus* can also accumulate and cause biofilm formation on medical devices, including artificial heart valves or joints, heart pacemakers and catheters [1].

S. aureus is also a rare cause of urinary tract infections. According to the literature, it is isolated in around 0.2–4% of urinary cultures. *S. aureus* bacteriuria (SABU) is encountered in patients with long-term care, catheters, urological abnormalities and procedures, older age, and comorbidities [1]. It is not clear the clinical significance of SABU and the treatment decision due to the possibility that it may be caused by contamination, colonization, asymptomatic bacteriuria, primary urinary tract infection or the manifestation of an invasive disease. There was a relationship between SABU and *S. aureus* bacteremia (SAB) and invasive staphylococcal disease [1]. Management of SABU was an unrecognized entity. For this reason, this study aimed to evaluate the patients with *S. aureus* isolated in urine cultures in an oncology hospital and contribute to the appropriate therapy or control of *S. aureus* urinary tract infections with or without bacteremia.

Materials and Methods

Our study included 82 adult (≥18 years old) with *S. aureus* urine isolation who were admitted or hospitalized at Ankara Oncology Trainig and Research Hospital between January 1, 2020 and July 1, 2023. Patient data was analyzed retro-spectively. This study was undertaken with the permission of the local ethical committee (20023-12/128). Demographic characteristics (age, gender) and clinical data (presence of hospital or community acquired infection, comorbidity, cancer, urinary stone history, urinary catheter use) and laboratory reports [bacterial culture, antibiogram, serum CRP (C-reactive protein) and procalcitonin levels] of the patients were analyzed. Antibiotic sensitivities of *S. aureus* and the number of leukocytes in the complete urinalysis were also evaluated. Data was collected on blood cultures taken within three months of urine samples and any positive blood cultures taken within one year. Among the patients with more than one culture positivity, only the first positive sample was included in this study. Patients with signs of infection other than SABU and/or SAB were excluded from the study.

The urine and nephrostomy samples were sent to the microbiology laboratory and were

Table 1. Antibiotic susceptibility of patients according to distribution to patient situation. (inpatient/outpatient

Patient situations	Benzyl penicillin (%)	Levo-floxacin (%)	Fosfo-mycin (%)	Cipro-floxacin (%)	Nitro-furantoin (%)	Trimethoprim-sulfa-methoxazole (%)	Linezolıd (%)	Vanco-mycin (%)	Teicoplanin (%)
Inpatient	3/22 (13.63)	8/12 (66.66)	12/14 (85,71)	8/12 (66,66)	13/15 (86,66)	20/22 (90,90)	20/20 (100)	22/22 (100)	22/22 (100)
Outpatient	1/14 (7.14)	26/32 (81,25)	30/35 (85,71)	21/22 (95,45)	42/42 (100)	59/59 (100)	44/44 (100)	60/60 (100)	60/60 (100)
Total	4/36 (11.11)	34/44 (77,27)	42/49 (85,71)	29/34 (85,29)	55/57 (96,44)	79/81 (97,53)	64/64 (100)	82/82 (100)	82/82 (100)

Patients with signs of infection other than SABU and/or SAB were excluded from the study.

The urine and nephrostomy samples were sent to the microbiology laboratory and were inoculated into 5% sheep blood agar and Eosin Methylene Blue (EMB) agar media and evaluated after overnight incubation by detecting bacterial colony numbers (CFU/mL). Blood samples were inoculated into the blood culture bottles and incubated in Autobio BC120 Device (Autobio-diagnostic, China). Automated system (VITEK, Biomerioux, France) and conventional methods were used for the typing of microorganisms and antibiotic susceptibility tests. The antibiotic susceptibility results were evaluated according to EUCAST (European Committee on Antimicrobial Susceptibility) criteria [2]. SABU was defined as "the detection of *S. aureus* in a urine sample, independent of co-detected pathogens" [1,3]. Analyses of contingency tables were evaluated by the chi-square test.

Data were analyzed using SPSS (version 26) (SPSS Inc., Chicago, IL, USA) and expressed as numbers, percentages, medians, minimums, and maximums.

Results

S. aureus was isolated from the urine of 82 patients. Of the patients, 43 (52%) were male and 39 (48%) were female. The age range of the patients was 0-90 years old and the average age was 53.84. The sample distribution was as follows: 74 (90,25%) mid-stream urine samples and eight (9,75%) nephrostomy samples. Among the patients, 22 (26.82%) were inpatients and 60 (73.17%) were outpatients. The antibiotic susceptibilities of patients are shown in Table 1.

All inpatients (n=22, 26.82%) had health care-related infections according to the Centers for Disease Control and Prevention (CDC) criteria [4]. A total of 43 (52%) patients had a symptomatic urinary tract infection.

The comorbidity status of the 82 patients was evaluated: 24 (29.26%) had bladder or kidney disease (hydronephrosis, ureter anomalies, ureteral stones, bladder stones), 20 (24.39%) had benign prostatic hyperplasia (BPH), 13 (15.85%) had hypertension, 10 (12.19%) had a history of kidney stone, nine (10.97%) had diabetes mellitus, three (3.65%) had renal cyst, and two (2.43%) had a central catheter. The immunosuppressive status of the patients was as follows: 17.07% (14/82) prostate cancer, 8.53% (7/82) bladder malignant neoplasm, 7.31% (6/82) cervix cancer, 6.09% (5/82) breast cancer, 3.65% (3/82) ovary cancer, 3.65% (3/82) stomach cancer, 2.43% (2/82) kidney cancer, 2.43% (2/82) rectum/colon cancer, 2.43% (2/82) lymphoma, 1.21% (1/82) esophagus malignant neoplasm, 1.21% (1/82) acute myeloid leukemia (AML), 1.21% (1/82) anal canal malignant neoplasm, 1.21% (1/82) soft tissue tumor, 1.21% (1/82) lung cancer, 1.21% (1/82) brain tumor, 1.21% (1/82) larynx tumor 1.21% (1/82) bone and connective tissue tumor.

Table 2. Characteristics of *Staphylococcus aureus* bacteriuria patients with simultaneous growth of *S. aureus* in blood cultures

No	Age	Gender	Comorbidity	Cancer	Urinary catheter	CRP (mg/L)	Procalcitonin (ng/ml)	WBC Urine (WBC /HPF)	Methicillin susceptibility
1	42	female	History of stones	Cervix neoplasm	Yes	146.47	0.264	11	susceptible
2	68	male	No	Bladder malignant neoplasm	Yes	66.06	0.279	40	susceptible
3	69	female	History of diabetes and urinary stones	No	Yes	197	6.31	312	susceptible
4	78	male	Hypertension	Prostat malignant neoplasm	Yes	208	0.176	24	resistant
5	87	female	Renal cyst	No	Yes	95.53	0.146	128	resistant

Totally, 63.4% (52/82) of the patients had cancer. A total of 56 (68.2%) of the patients had urological abnormalities, and 15 patients (18.2 %) had urinary catheter use.

The colony count was more than 105 CFU/mL in 45% (37/82) of the urine samples. Among the *S. aureus* isolates from urine, 39.02% (32/82) were resistant to methicillin. Antibiotic susceptibilities were as follows: benzyl penicillin 11.11% (4/36), levofloxacin77.27% (34/44), fosfomycin 85.71% (42/49), ciprofloxacin 85.29% (29/34), nitrofurantoin 96.49% (55/57), trimethoprim-sulfamethoxazole 97.53% (79/81) and linezolid 100% (64/64). All isolates were susceptible to vancomycin and teicoplanin.

In SABU patients' urinalysis indicated that white blood cell count ranged between 0 and 220.6 WBC/HPF; the mean was 152.46. Patients' CRP levels in serum ranged between 0.38 and 299.25 mg/L; the average was 62.17. Patients' procalcitonin levels in serum ranged between 0.019 and 6.31 ng/ml, (average 0,3656). SABU+SAB patients' CRP levels in serum ranged between 66.06 and 208 mg/L, (average 142.6). Patients' procalcitonin levels in serum ranged between 0.146 and 6.31 ng/ml, (average1.43). Patients with symptomatic UTIs were more likely to have significant pyuria than those who were asymptomatic (P=0.013).

Of the 82 patients with *S. aureus* growth in their urine sample, five hospitalized patients (6.09%) had simultaneous *S. aureus* growth in the blood culture. All of this bacteremia (5/5) occurred after urological instrumentation or catheterization and is considered secondary to seeding from bacteriuria. The characteristics of patients with simultaneous growth of *S. aureus* in their blood cultures are shown in Table 2.

Discussion

S. aureus is a major cause of both hospital-acquired and community-acquired bloodstream infections. The mortality rate associated with *S. aureus* bacteremia might reach 40%. In patients receiving antibiotic therapy and prolonged hospitalisations, *S. aureus* can cause complex infections, such as endocarditis. *S. aureus* is an infrequent cause of bacteriuria. The presence of *S.aureus* in urine samples can be attributed to contam-

ination, colonisation, urinary tract infection, bacteremic seeding from another location or *S. aureus* bacteremia. Urinary colonisation or infections caused by *S. aureus* were frequently observed in individuals who had indwelling catheters or recent urinary tract instrumen-tations. The reported prevalence of *S. aureus* isolation from urinary tract infections (UTIs) ranged from 0.5% to 1% [5].

There is limited guidance available regarding the examination and treatment of *S. aureus* bacteriuria. Schuler F et al. [3] identified urinary tract catheterization as the primary contributing factor for SABU, accounting for 63-82% of cases. Other factors include urinary tract obstruction, invasive procedures, recent hospitalisation, old age, and male gender [3]. On the other hand, *S. aureus* is often found on both the skin and mucous membranes at the same time in people with SABU, which means that there is a higher chance of contamination during sampling (66-75%) [1]. Our investigation on SABU patients found no statistically significant difference between male and female patients related to *S. aureus* bacteriuria. In our study, 26.82% of the SABU patients were admitted as inpatients, whereas 73.17% received treatment as outpatients. The patients in our study had several comorbidities and half of our patients had cancers. 18.2% of SABU patients had urinary catheters, while 68.2% had urological abnormalities. These data recognized that urological abnormalities and urinary catheters were significant underlying factors in SABU patients; in such patients' measures including decolonization, antibiotic treatment, and avoiding catheterization may be beneficial.

According to the literature, SAB may be a cause or a result of SABU. SABU might serve as the focal site for future bacteremia and invasive infection [6]. The incidence of concurrent SAB in patients with SABU has been reported to range from 8% to 27%, and it has been associated with poor outcomes. The established risk factors associated with simultaneous SAB include being male, being hospitalised, having signs of systemic infection, having urinary tract abnormalities, and having diabetes [1]. In a study conducted by Mason et al.[1], it was found that bacteremia developed in four of the six patients who had urological instrumentation in the SABU group [1]. Arpi and Renneberg [7] discovered that out of 132 hospitalised patients with SABU, 8.3% experienced the development of SAB. They hypothesised that the development of secondary SAB to SABU was linked to urinary catheterization, urological abnormalities, and instrumentation [7]. According to a study conducted by Al Mohajer et al.[8], among 326 patients with SABU, SAB occurred in 22% of patients with MRSA SABU and 8.4% of patients with MSSA SABU within a period of 12 months. The risk factors for developing invasive disease were the absence of UTI symptoms and being admitted as an inpatient [8]. A meta-analysis conducted by Schuler F et al.[3] found that simultaneous SABU was recorded in 7.8-39% of SAB patients [3]. Additionally, the study group conducted a combined analysis and discovered a strong correlation between SABU and infections in the bones and joints, as well as the occurrence of septic embolism in the spleen, kidneys, or central nervous system [3]. Furthermore, it was documented that SABU could occur as a consequence of SAB, and this was identified as an independent risk factor for mortality. If there are no identifiable risk factors for colonisation, the presence of SABU might indicate the presence of an invasive illness, such as infective endocarditis. The presence of SABU in infective endocarditis can represent a more severe result and may indicate vasculitis spread manifested by renal microabscesses [1]. In our study, we found that 6.9% of patients with SABU had SAB. Additionally, four out of the five patients with both SABU and SAB had urinary catheters which correlates with the information reported in the literature. We proposed that the

probability of SAB development was greater in patients with genitourinary operations (catheterization) and malignancy. Pre-emptive antibiotic treatment in patients prior to instrumentation was recommended by studies [1]. We proposed that extensive clinical trials involve a greater number of patients.

There was a lack of clear instructions about the investigation and management of SABU, including the most effective antibiotic treatment. In Mason et al.[1]'s study, 37% of patients with SABU showed symptoms of urinary tract infection, although 57% of them were prescribed antibiotics [1]. In our study, 52% of patients had a symptomatic urinary tract infection, and 56% of patients had received antibiotic treatment. Within a three-month period, none of the patients exhibited a recurrence of *S. aureus* in their urine culture after testing positive initially. These data indicated that the antibiotic treatment decision of SABU was a significant problem. The differential diagnosis of asymptomatic bacteriuria, colonisation, UTI, and bacteriuria potentially linked with bacteremia should rely on clinical evidence and the presence of pyuria in patients with various risk factors. In order to limit the inappropriate administration of antibiotics, we recommended doing repeated urine and blood cultures for individuals with suspected asymptomatic SABU.

Effective medicines for the treatment of MSSA include intravenous administration of Cefazolin or Flucloxacillin. For MRSA, effective treatment options include Vancomycin, Linezolid, or Daptomycin [3]. In our study, we found that 39.02% of the *S. aureus* isolates from urine were resistant to methicillin. Among the group of patients with SABU+SAB (n=5) in our investigation, two patients were found to have MRSA SABU. While MRSA SABU seemed to have a stronger connection to SAB than MSSA SABU, our investigation demonstrated that patients infected with MSSA were susceptible to both SABU and SAB. We recommend that the choice of antibiotics should be based on the local susceptibility patterns of each hospital. In our study, there was a low level of resistance to usual first-line antibiotics.

In conclusion, our study revealed that the investigation and management of *S. aureus* bacteriuria is challenging. Further studies with a larger sample size are necessary. Urological abnormalities, cancers and urinary catheters are significant underlying factors in SABU patients; in such patients' measures including decolonization, antibiotic treatment, and avoiding catheterization may be beneficial. Pre-emptive antibiotic treatment in patients prior to instrumentation is recommended. The differential diagnosis of asymptomatic bacteriuria, colonization, UTI and bacteriuria potentially associated with bacteremia should be based on clinical data and presence of pyuria. To avoid unnecessary antibiotic use, we suggest repeated urine and blood cultures for SABU patients. The microbiology results may be useful in guiding clinicians for SABU patients.

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