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Original Article

Evaluation of Patients with *Staphylococcus aureus* Bacteriuria Over a Three-year Period in an Oncology Hospital

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ABSTRACT

Aim: *Staphylococcus aureus* bacteriuria (SABU) is encountered in patients with long-term care, urologic abnormalities, older age, and comorbidities. SABU may be caused by contamination, colonization, asymptomatic bacteriuria, urinary tract infection (UTI), or invasive disease, but its clinical relevance and therapy are unclear. This study evaluated individuals with *S. aureus* isolated via urine culture at an oncology hospital.

Methods: Eighty-two patients with *S. aureus* urine isolation were studied retrospectively. Age, sex, clinical data, and laboratory results were evaluated. Concurrent *S. aureus* bacteremia (SAB) development was also determined.

Results: Of the patients, 52% were male and 48% were female. Overall, 63.4% of the patients had cancer. Among these patients, 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). Moreover, 68.2% of the patients had urological abnormalities, and 18.2% had urinary catheters. Moreover, 39.02% of *S. aureus* were resistant to methicillin. The average C-reactive protein level in SABU patients was 62.17 mg/L and procalcitonin was 0.3656 ng/mL. Five of the SABU patients (6.09%) had simultaneous *S. aureus* in their blood cultures, and all of the infections were secondary to bacteriuria and seeding following urological instrumentation/catheterization.

Conclusion: Urological abnormalities/cancers and urinary catheter use were significant underlying factors of SABU. The differential diagnosis of SABU should be based on clinical/laboratory data and presence of pyuria. To avoid unnecessary antibiotic use, repeated urine and blood cultures may be useful for guiding clinicians about the use of SABU.

Keywords: *Staphylococcus aureus,* bacteriuria, methicillin resistance

Introduction

Staphylococcus aureus infections are a significant cause of mortality and morbidity in immunosuppressed patients. *S. aureus* is present in about 20-30% of the nose and skin of healthy adults. These percentages are higher for hospitalized patients and hospital staff. *S. aureus* infections range from mild to life-threatening infections, including skin infections, abscesses, bacteremia, endocarditis, osteomyelitis, and pneumonia. *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 infection (UTI). According to the literature, *S. aureus* bacteriuria (SABU) is isolated in approximately 0.2-4% of urinary cultures. SABU is encountered in patients with long-term care, catheterization, urologic 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

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bacteriuria, primary UTI, or the manifestation of an invasive disease. There is a relationship between SABU and *S. aureus* bacteremia (SAB) and invasive staphylococcal disease [1]. The management of SABU was an unrecognized entity. For this reason, this study aimed to evaluate patients with *S. aureus* isolated via urine cultures in an oncology hospital and to contribute to appropriate therapy or control of *S. aureus* UTIs with or without bacteremia.

Methods

Our study included 82 adult (≥18 years old) with *S. aureus* urine isolation who were admitted or hospitalized at University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between January 1, 2020, and July 1, 2023. Patient data were analyzed retrospectively. This study was conducted with the permission of the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Local Ethics Committee (research no.: 2023-12/128, date: 11.01.2024). 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 C-reactive protein (CRP) and procalcitonin levels] of the patients were analyzed. Antibiotic sensitivities to *S. aureus* and the number of leukocytes in the complete urinalysis were also evaluated. Data were collected on blood cultures obtained within three months from urine samples and any positive blood cultures obtained within one year. Among 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 infection were excluded from the study.

Urine and nephrostomy samples were sent to the microbiology laboratory and inoculated into 5% sheep blood agar and eosin methylene blue agar media and evaluated after overnight incubation by detecting bacterial colony numbers (CFU/mL). Blood samples were inoculated into blood culture bottles and incubated in an Autobio BC120 device (Autobio-diagnostic, China). An 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 European Committee on Antimicrobial Susceptibility Testing criteria [2]. SABU was defined as "the detection of *S. aureus* in a urine sample, independent of co-detected pathogens" [1,3]. The analyses of the contingency tables were performed using the chi-square test.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (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. Among the included patients, 43 (52%) were male and 39 (48%) were female. The age of the patients ranged from 0 to 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 included patients, 22 (26.82%) were inpatients and 60 (73.17%) were outpatients. The antibiotic susceptibilities of the patients are presented in Table 1.

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

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, 13 (15.85%) had hypertension, 10 (12.19%) had a history of kidney stones, nine (10.97%) had diabetes mellitus, three (3.65%) had renal cysts, 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, 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. In total, 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.

Colony counts were $>10^5$ 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); levofloxacin, 77.27% (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.

The urinalysis results of patients with SABU indicated that white blood cell count ranged between 0 and 220.6 white blood cell/HPF; the mean was 152.46. The serum CRP levels ranged from 0.38 to 299.25 mg/L; the average was 62.17. Patients' procalcitonin levels in serum ranged from 0.019 to 6.31 ng/mL, (average 0,3656). SABU+SAB patients' CRP levels in serum ranged from 66.06 to 208 mg/L, (average 142.6). Patients' procalcitonin levels in serum ranged from 0.146 to 6.31 ng/mL, (average 1.43). Patients with symptomatic UTI were more likely to have significant pyuria than those who were asymptomatic (p=0.013).

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

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

Patient situations	Benzyl penicillin (%)	Levofloxacin (%)	Fosfomycin (%)	Ciprofloxacin (%)	Nitrofurantoin (%)	Trimethoprim-sulfamethoxazole (%)	Linezolid (%)	Vancomycin (%)	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)

Table 2. Characteristics of patients with *Staphylococcus aureus* bacteriuria and simultaneous *S. aureus* growth 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

CRP: C-reactive protein, WBC: White blood cell

Discussion

S. aureus is a major cause of hospital- and community-acquired bloodstream infections. The mortality rate associated with SAB might reach 40%. In patients receiving antibiotic therapy and prolonged hospitalization, *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 contamination, colonization, UTI, bacteremic seeding from another location or SAB. Urinary colonization or infections caused by *S. aureus* were frequently observed in individuals who received indwelling catheters or recent urinary tract instrumentation. The reported prevalence of *S. aureus* isolates from UTIs ranges from 0.5% to 1% [5].

Limited guidance is available regarding the examination and treatment of SABU. Schuler et al. [3] identified urinary tract catheterization as the primary contributor to SABU, accounting for 63-82% of cases. Other factors include urinary tract obstruction, invasive procedures, the recent hospitalization, 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, indicating a higher risk of contamination during sampling (66-75%) [1]. Our investigation of patients with SABU found no statistically significant differences between male and female patients with SABU. 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 urologic abnormalities. These data recognized that urologic abnormalities and urinary catheters were significant underlying factors in SABU patients; measures for such patients, including decolonization, antibiotic treatment, and catheterization, may be beneficial.

According to the literature, SAB may be a cause or a result of SABU. SABU may serve as the focal site for future bacteremia and invasive infection [6]. The incidence of concurrent SAB in patients with SABU ranges from 8% to 27% and is associated with poor outcomes. The established risk factors associated with simultaneous SAB include male sex, hospitalization, signs of systemic infection, urinary tract abnormalities, and diabetes [1]. In a study conducted by Mason et al. [1], it was found that bacteremia developed in four of six patients who underwent urological instrumentation in the SABU group [1]. Arpi and Renneberg [7] found that out of 132 hospitalized patients with SABU, 8.3% experienced the development of SAB. They hypothesized that the development of secondary SAB to SABU was linked to urinary catheterization, urologic 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 12 months. The risk factors for developing invasive disease were absence of UTI symptoms and admission as an inpatient [8]. A meta-analysis conducted by Schuler 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 bones and joints, as well as the occurrence of septic embolism in the

spleen, kidneys, or central nervous system [3]. Furthermore, 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 colonization, the presence of SABU might indicate the presence of an invasive illness, such as infective endocarditis. The presence of SABU in infective endocarditis can be a more severe result and may indicate the spread of vasculitis 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 undergoing genitourinary operations (catheterization) and malignancy. Pre-emptive antibiotic treatment in patients prior to instrumentation has been recommended in previous studies [1]. We propose that extensive clinical trials should involve a greater number of patients.

There was a lack of clear instructions regarding the investigation and management of SABU, including the most effective antibiotic treatment. In Mason et al.'s [1] study, 37% of patients with SABU showed symptoms of UTI, although 57% were prescribed antibiotics [1]. In our study, 52% of patients had a symptomatic UTI, and 56% received antibiotic treatment. Within a 3-month period, none of the patients exhibited a recurrence of *S. aureus* based on urine culture results after a positive initial test. These data indicated that the selection of antibiotic treatment for SABU was a significant problem. The differential diagnosis of asymptomatic bacteriuria, colonization, UTI and bacteriuria potentially linked with bacteremia should rely on clinical evidence and the presence of pyuria in patients with various risk factors. To limit inappropriate antibiotic administration, we recommend repeated urine and blood culture for individuals with suspected asymptomatic SABU.

Effective medicines for MSSA include intravenous cefazolin or flucloxacillin. Effective treatment options for MRSA include vancomycin, linezolid, and daptomycin [3]. In our study, 39.02% of *S. aureus* isolates from urine were resistant to methicillin. Among the group of patients with SABU+SAB (n=5) in our investigation, two were found to have MRSA SABU. Although MRSA SABU appeared to have a stronger connection with SAB than MSSA SABU, our investigation demonstrated that patients infected with MSSA were susceptible to both SABU and SAB. We recommend that the selection of antibiotics should be based on the local susceptibility patterns of each hospital. In our study, there was low resistance to usual first-line antibiotics.

Studys Limitations

The retrospective nature of our research and the small sample size are its limitations.

Conclusion

In conclusion, our study revealed that the investigation and management of SABU are challenging. Further studies with larger sample sizes are necessary. Urological abnormalities, cancers, and urinary catheters are significant underlying factors in SABU patients; measures for such patients, including decolonization, antibiotic treatment, and avoidance of 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 the presence of pyuria. To avoid unnecessary antibiotic use, we recommend repeated urine and blood culture for patients with SABU. The microbiology results may be useful for guiding clinicians about SABU.

Ethics

Ethics Committee Approval: This study was conducted with the permission of the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Local Ethics Committee (research no: 2023-12/128, date: 11.01.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.B, T.U, G.İ, M.D, A.P., Concept: M.D, T.D., Design: M.D, T.D., Data Collection or Processing: M.D, T.D., Analysis or Interpretation: M.D, T.D., Literature Search: İ.M, S.S.Y, A.S.G, N.İ., Writing: M.D, T.D, A.S.G.

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