Clinical Characteristics of Patients with *Staphylococcus aureus* Bile Infection

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ABSTRACT **Background:** The hepatobiliary system is a sterile micro-environment. Bacterial infection in this system is most commonly associated with anaerobes as well as gram-positive and gram-negative bacteria. Biliary infections with *Staphylococcus aureus* are poorly characterized.

Objectives: To depict the clinical characteristics and outcome of patients with *S. aureus* infection of the hepatobiliary system.

Methods: Medical records of patients with bile cultures positive for *S. aureus* from January 2006 to November 2020 were extracted from the computerized database of a hospital in Israel.

Results: We analyzed the results of 28 cases that were found in the database. The mean age of study patients was 62.2 ± 19 years. Hypertension, dyslipidemia, chronic kidney disease, diabetes, and benign prostatic hypertrophy were the most common co-morbidities (57.1%, 32.1%, 25%, 25%, and 25%, respectively). Fourteen of the methicillin-resistant *S. aureus* (MRSA) bile cultures (82.3%) were a result of primary S. aureus biliary infections (no other source for *S. aureus* infection) and the remainder were of a secondary infection. Eight of the MRSA cultures (47.1%) were from hospital acquired infections. Increased hospital mortality in patients with *S. aureus* hepatobiliary infection was associated with hypertension (P = 0.04), bedridden status (P = 0.01), and nursing home residence (P = 0.003).

Conclusions: Hepatobiliary infection with *S. aureus* can manifest in a variety of ways. *S. aureus* should be especially considered in patients who are bedridden, present with hypertension, or live in nursing homes because of their association with in-hospital mortality resulting from this entity.

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KEY WORDS: bile, bile culture, biliary tract, cholecystitis, *Staphylococcus aureus*

Staphylococcus aureus is a gram-positive bacterium and a component of the normal human flora. It is most commonly located on the human skin and mucous membranes and can cause various infections, such as skin and soft tissue infections, septic arthritis, osteomyelitis, endocarditis, and pneumonia. However, the biliary tract is rarely involved. Previous studies showed isolation of *staphylococcus aureus* in 0.8–5.6%% of bile cultures in patients undergoing cholecystectomy [1].

Infections of the biliary tract are conventionally associated with obstruction of the biliary tract due to solid tumors or biliary stones and subsequent infection. Common pathogens include anaerobes as well as gram-positive and gram-negative bacteria [2]. Management of biliary tract infection typically includes rapid antibiotic therapy and biliary drainage. Proper and prompt management of this infection is associated with improved prognosis [3-5].

Despite the substantial morbidity and mortality attributed to this virulent pathogen and the wide array of possible clinical presentations, the clinical characteristics of patients with *S. aureus* biliary infections are yet to be elucidated. We designed and conducted a study to provide a better understanding of the clinical characteristics of biliary tract infections caused by *S. aureus* in patients admitted to a single tertiary care center in Israel over the course of 14 years.

PATIENTS AND METHODS:

A retrospective cohort study of 28 patients with positive *S. aureus* bile cultures was conducted at Shaare Zedek Medical Center, a 1000- bed tertiary referral center in Jerusalem, Israel, between 1 January 2006 and 1 November 2020. We reviewed the medical records of all adult patients with positive *S. aureus* bile culture hospitalized during this 14-year span at internal and surgical departments at Shaare Zedek. Included were adult patients (≥ 18 years of age) with *S. aureus* growth in bile cultures for whom the relevant data were available. Patients younger than 18 years of age and those for whom no clinical or laboratory data were available in the hospital medical records were excluded. Bile cultures were obtained from biliary fluid or swab specimens.

The study received approval from the local ethics committee and was conducted according to the Helsinki declara-

tion. Collected data was encrypted and coded to preserve the privacy and anonymity of the patients in the study. Informed consent was waived due to the non-interventional nature of the study.

DATA COLLECTION

Epidemiologic, clinical, and laboratory data of all patients with laboratory-confirmed growth of *S. aureus* from bile cultures were extracted from each patient's medical records. The data were collected using a data extraction sheet and included demographical characteristics, social status, co-morbidities, antibiotic management, clinical outcomes, and laboratory test results at time of admission.

STUDY DEFINITIONS

Primary biliary infection was considered as an infection with *S. aureus* originating from the biliary tract with no other probable infection site. Whereas, secondary biliary infection was defined as an infection of the biliary tract, originating from a different infection site unrelated to the biliary tree.

Biliary infection characterized by a positive *S. aureus* bile culture from patients after more than 48 hours of hospitalization was considered nosocomial, in contrast to positive *S. aureus* bile cultures from patients within 48 hours of hospitalization, which was considered community- acquired.

Clinical outcomes were divided into subgroups of discharge and death within current hospitalization.

STATISTICAL ANALYSIS

Statistical analysis was performed using Epi-Info 7.2.4 software (CDC, USA) and further data analysis was conducted by Stata version 16.1 (StataCorp LLC, Texas, USA). Categorical variables were examined using the chi-square test or the Fisher exact test where applicable. Continuous variables were compared using the Student's *t*-test if normally distributed or Mann-Whitney test if not. To evaluate the association of different variables, univariate analysis was performed. Statistically associated variables ($P < 0.05$) were included in multivariate analysis. Statistical significance was set at $P < 0.05$.

RESULTS

CHARACTERISTICS OF STUDY COHORT

Between January 2006 and November 2020, 28 patients with confirmed *S. aureus* growth in bile cultures were hospitalized at Shaare Zedek Medical Center. The characteristics of the study cohort are outlined in Table 1.

The mean age of the cohort subjects was 62.2 ± 19 years, and 15 were males (53.6%). The most common co-morbidities were hypertension, dyslipidemia, chronic kidney disease, diabetes, and benign prostatic hypertrophy (57.1%, 32.1%, 25%,

Table 1. Clinical characteristics of the study participants

	N
Age (median, interquartile range), years	68 (55–79.5)
Sex	
Male	15 (53.6%)
Female	13 (46.4%)
Residence	
Nursing home	3 (10.7%)
Home	25 (89.3%)
Bedridden status	
Yes	4 (14.3%)
No	24 (85.7%)
Co-morbidities	
Hypertension	16 (57.1%)
Hyperlipidemia	9 (32.1%)
Diabetes mellitus	7 (25%)
Chronic kidney disease	7 (25%)
Liver disease	2 (7.1%)
Benign prostatic hypertrophy	7 (25%)
Previous cerebrovascular accident	6 (21.4%)
Immunosuppression	3 (10.7%)
Previous surgeries in last year	3 (10.7%)
Infection	
Primary	23 (82.1%)
Secondary	5 (17.9%)
Skin	4 (80%)
Myocardium	1 (20%)
Culture growth	
Single	9 (32.1%)
Mixed*	19 (67.9%)
Source of Infection	
Hospital acquired	18 (64.3%)
Community acquired	10 (35.7%)
Pathogen sensitivity	
Methicillin resistant	17 (60.7%)
Methicillin susceptible	11 (39.3%)
Hospitalization outcome	
Discharge	23 (82.1%)
Death	5 (17.9%)

*Bacteria found in addition to *S. aureus* in bile cultures included: *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia,* and *Enterobacter spp.*

25%, and 25% respectively). Seventeen bile cultures (60.7%) demonstrated growth of methicillin-resistant *Staphylococcus aureus* (MRSA).

Fourteen of the MRSA bile cultures (82.3%) were a result of primary *S. aureus* biliary infection and the remainder were of a secondary infection. In addition, eight of the MRSA cultures (47.1%) were hospital-acquired infections. Only three patients underwent abdominal procedures or surgery in the year prior to the infection, and none had biliary drains. The mean age of patients with positive MRSA bile cultures was 73.7 ± 18 years, nine (52.9%) were men, two (11.75%) were admitted from a nursing home, four (23.5%) were bedridden, and four (23.5%) died during their hospitalization.

COMPARISON BETWEEN PRIMARY AND SECONDARY *S. AUREUS* BILIARY INFECTIONS

Twenty-three study participants (82.1%) were diagnosed with primary *S. aureus* bile infection. The remaining five patients (17.9%) were diagnosed with a *S. aureus* bile infection secondary to an ongoing infection in another body site. The secondary infection of four participants was attributed to a concurrent skin infection, and the other infection to a myocardial abscess. A comparison between patients with primary and secondary *S. aureus* bile infection was conducted based on their clinical characteristics and outcome and did not reveal statistically significant differences between the two groups [Table 2].

FACTORS ASSOCIATED WITH DEATH IN *S. AUREUS* BILIARY INFECTIONS

Five study patients died during their hospitalization and a multivariate logistic regression was performed to ascertain the effects of age, social status, background illnesses, and microbiological findings on the endpoint of death during hospitalization. Univariate analysis revealed that age ($P = 0.003$), bedridden status ($P = 0.01$), and nursing home residence ($P = 0.003$) were all were associated with death during hospitalization. As anticipated, they were all significantly intercorrelated, and the major independent factor was nursing home residence [Table 3].

DISCUSSION

Acute biliary tract infection typically results from obstruction of its ducts, leading to inflammation and infection of the surrounding structures. In healthy individuals the biliary tract is a sterile system; however, in a setting of acute cholecystitis, approximately 50% of patients have positive bile cultures. Typical pathogens isolated from sites of biliary infection are gram-negative and gram-positive bacteria such as *Escherichia coli*, *Klebsiella* spp., and *Enterococcus spp.*, as well as anaerobes [6]. *S. aureus* infections are common in the community as well as in a hospital setting. The emergency of multi-drug resistant strains, such as MRSA, adds to the significant epidemiological burden and poses a unique treatment challenge for hospitals. *S. aureus* has been linked to various clinically important infections, such as septic arthritis, pneumonia, endocarditis, osteomyelitis, and skin and soft tissue infections [5,7]. Despite the wide array of infections caused by *S. aureus*, the biliary tract is rarely involved. In an extensive review of the literature regarding isolation of *S. aureus* from bile or gallbladder specimens of patients with biliary diseases, we found only six studies that described the association [8-13].

Lou et al. [8] retrospectively examined the results of bile cultures obtained during biliary tract surgery between 1975 and 1976. Of 74 patients, only one had growth of *S. aureus* in his bile culture. Brook [9] performed a similar retrospective analysis of organism recovery from biliary tract specimens. His research was conducted during 4 consecutive years in two military hospitals. Although 123 bile specimens were obtained, and 286 organisms were isolated, *S. aureus* was isolated in only 1 culture. *Fukunaga's* [10] research focused on bile cultures in patients undergoing cholecystectomy. Positive bile cultures were found in 46.7% of 501 cases but only seven bile cultures yielded *S. aureus.*

We concluded that hypertension, bedridden status, and nursing home residence are all associated with an increase in hospital mortality due to *S. aureus* biliary infection. These risk factors were not described in the literature and our cohort provides a new outlook on clinically important patient characteristics. Interestingly, no statistically significant differences were seen between patients infected with MRSA and methicillin sensitive *S. aureus* strains with regards to mortality, which contrasts with the results reported from previous studies [14]. We believe that this finding could be at least partially explained by the overall increased mortality in our cohort.

Immunosuppression and diabetes are commonly associated with *S. aureus* infection and bacteremia [15], yet less than one-third of the participants in our study presented with diabetes, and only three participants were immunosuppressed. Moreover, old age, dyslipidemia, chronic kidney disease, and male gender, all considered to be proven risk factors for a more severe disease course in previous studies, were not found to have a significant correlation to severity in our study [16].

The majority of bile cultures positive for *S. aureus* in our study were of mixed growth with another bacteria (n=19, 67.9%), a finding that was not described in previous studies and reviews [6].

LIMITATIONS

Our study has several limitations; namely the inherent limitation of relatively small sample size, the retrospective single-center design, and the polymicrobial nature of infection in most subjects. In addition, no testing was performed for nasal carriage of *S. aureus*, which is known to increase the likelihood for invasive staphylococcal infections among susceptible individuals.

Table 2. Statistical comparison of variables between primary and secondary *Staphylococcus aureus* bile infection

Variable	Primary infection n=23	Secondary infection n=5	*P* value
Age, years (median, interquartile range)	68 (55–81)	70 (26–71)	0.08
Sex			
Male	11 (73.3%)	4 (26.7%)	0.21
Female	12 (92.3%)	1 (7.7%)	
Living arrangement			
Nursing home	2 (66.7%)	1 (33.3%)	0.46
Private home	21 (84%)	4 (16%)	
Bedridden status			
Yes	3 (75%)	1 (25%)	0.57
No	20 (83.3%)	4 (16.7%)	
Hypertension			
Yes	13 (81.25%)	3 (18.75%)	0.64
No	10 (83.3%)	2 (16.7%)	
Hyperlipidemia			
Yes	7 (78.8%)	2 (21.2%)	0.53
No	16 (84.2%)	3 (15.8%)	
Chronic kidney disease			
Yes	6 (85.7%)	1 (14.3%)	0.63
No	17 (81%)	4 (19%)	
Liver disease			
Yes	2 (100%)	0 (0%)	0.67
No	21 (81%)	5 (19%)	
Benign prostatic hypertension			
Yes	6 (85.7%)	1 (14.3%)	0.63
No	17 (81%)	4 (19%)	
Previous cerebrovascular disease			
Yes	5 (83.3%)	1 (16.7%)	0.71
No	18 (81.8%)	4 (18.2%)	
Diabetes mellitus			
Yes	5 (71.4%)	2 (28.6%)	0.37
No	18 (85.7%)	3 (14.3%)	
Immunosuppression			
Yes	3 (100%)	0 (0%)	0.54
No	20 (80%)	5 (20%)	
Specimen type			
Bile fluid	19 (82.6%)	4 (17.4%)	0.71
Bile swab	4 (80%)	1 (20%)	
Single or mixed growth in culture			
Single	8 (88.9%)	1 (11.1%)	0.47
Mixed	15 (78.9%)	4 (21.1%)	
Outcome			
Favorable	19 (82.6%)	4 (17.4%)	0.65
Mortality	4 (80%)	1 (20%)	
Hospital acquired infection			
Yes	15 (83.3%)	3 (16.7%)	0.60
No	8 (80%)	2 (20%)	
Previous surgeries in last year			
Yes	1 (33.3%)	2 (66.7%)	0.07
No	22 (88%)	3 (12%)	
Methicillin resistant pathogen			
Yes	14 (82.4%)	3 (17.6%)	0.67
No	9 (81.8%)	2 (18.2%)	

Table 3. Statistical analysis of in-hospital mortality in relation to patient characteristics

Variable	Alive n=23	Deceased n=5	Univariate analysis *P* value
Age, years (median, interquartile range)	64 (52–75)	86 (78–88)	**0.003**
Sex			
Male	11 (73.3%)	4 (26.7%)	0.21
Female	12 (92.3%)	1 (7.7%)	
Bedridden			
Yes	1 (25%)	3 (75%)	**0.01**
No	22 (92%)	2 (8%)	
Benign prostatic hyperplasia			
Yes	4 (57.1%)	3 (42.9%)	0.08
No	19 (90.5%)	2 (9.5%)	
Chronic kidney disease			
Yes	4 (57.1%)	3 (42.9%)	0.08
No	19 (90.5%)	2 (9.5%)	
Previous cerebrovascular accident			
Yes	4 (57.1%)	2 (42.9%)	0.28
No	19 (86.4%)	3 (13.6%)	
Diabetes mellitus			
Yes	4 (57.1%)	3 (42.9%)	0.08
No	19 (90.5%)	2 (9.5%)	
Hyperlipidemia			
Yes	6 (66.7%)	3 (33.3%)	0.17
No	17 (89.5%)	2 (10.5%)	
Hypertension			
Yes	11 (68.75%)	5 (31.25%)	0.053
No	12 (100%)	0 (0%)	
Liver disease			
Yes	1 (50%)	1 (50%)	0.33
No	22 (84.6%)	4 (15.4%)	
Hypothyroidism			
Yes	2 (100%)	0 (0%)	0.67
No	21 (80.8%)	5 (19.2%)	
Immunosuppression			
Yes	3 (100%)	0 (0%)	0.54
No	20 (80%)	5 (20%)	
Previous surgeries in the last year			
Yes	2 (66.7%)	1 (33.3%)	0.46
No	21 (84%)	4 (16%)	
Primary or secondary bile infection			
Primary	19 (82.6%)	4 (17.4%)	0.66
Secondary	4 (0.8%)	1 (0.2%)	
Hospital acquired infection			
Yes	15 (83.3%)	3 (16.7%)	0.6
No	8 (80%)	2 (20%)	
Specimen			
Biliary fluid	19 (79.2%)	5 (20.8%)	0.43
Biliary swab	4 (100%)	0 (0%)	
Methicillin resistant pathogen			
Yes	13 (76.5%)	4 (23.5%)	0.33
No	10 (90.9%)	1 (9.1%)	

Bold indicates significance

Our study also has several strengths as it is the largest study available to date that accurately characterizes *S. aureus* biliary tract infections. We think it adds valuable information on an important and not often considered entity.

CONCLUSIONS

Older age, bedridden status, and nursing home residence are predicting factors for the clinical outcome of *S. aureus* biliary infection.

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Too much sanity may be madness. And maddest of all, to see life as it is and not as it should be!
Miguel de Cervantes (1547–1616), Spanish writer

Capsule

Anti-inflammatory clearance of amyloid-β by a chimeric Gas6 fusion protein

Clearing amyloid-β (Aβ) through immunotherapy is one of the most promising therapeutic approaches to Alzheimer's disease (AD). Although several monoclonal antibodies against Aβ have been shown to substantially reduce Aβ burden in patients with AD, their effects on improving cognitive function remain marginal. In addition, a significant portion of patients treated with Aβ-targeting antibodies experience brain edema and microhemorrhage associated with antibody-mediated Fc receptor activation in the brain. **Jung** and colleagues developed a phagocytosis inducer for Aβ consisting of a single-chain variable fragment of an Aβ-targeting monoclonal antibody fused with a truncated receptor binding domain of growth arrest-specific 6 (Gas6), a bridging molecule for the clearance of dead cells via TAM (TYRO3, AXL, and MERTK) receptors. This chimeric fusion protein (αAβ-Gas6) selectively eliminates Aβ plaques through TAM receptor-dependent phagocytosis without inducing NF-kB-mediated inflammatory responses or reactive gliosis. Furthermore, αAβ-Gas6 can induce synergistic clearance of Aβ by activating both microglial and astrocytic phagocytosis, resulting in better behavioral outcomes with substantially reduced synapse elimination and microhemorrhage in AD and cerebral amyloid angiopathy model mice compared with Aβ antibody treatment. These results suggest that αAβ-Gas6 could be a novel immunotherapeutic agent for AD that overcomes the side effects of conventional antibody therapy.

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