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Clinical Characteristics and Outcome of *Chryseobacterium indologenes* Bacteremia

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Background: *Chryseobacterium indologenes*, although widely distributed in nature, is a rare human pathogen. This study aims to analyze the clinical characteristics, risk factors, and outcome of patients with *C. indologenes* bacteremia. **Methods:** A retrospective study was conducted from January 1, 2002 to April 30, 2011 analyzing patients with *C. indologenes* bacteremia at a medical center in northern Taiwan. **Results:** Forty-eight episodes of *C. indologenes* bacteremia in 47 patients were identified. Among all bacteremic episodes, 44 (92%) were nosocomial, three (6%) were healthcare-associated, and only one (2%) was community-acquired. Thirty-three episodes (69%) were primary bacteremia, and nine (19%) were from pneumonia. Forty-one isolates (85%) were non-susceptible to imipenem, and only 20% (3/15) were non-susceptible to flomoxef. Patients with tunneled catheter, delayed onset of bacteremia, isolates were non-susceptible to ceftazidime or cefepime and potentially associated with higher mortality. Pneumonia (OR = 31.359; 95% CI = 1.35-729.39; $p = 0.032$) and non-susceptibility to ceftazidime (OR = 21.057; 95% CI = 2.28-194.57; $p = 0.007$) were independent risk factors for in-hospital mortality. **Conclusions:** The emergence of *C. indologenes* bacteremia has had a great clinical impact on inpatient care. It is important to identify the clinical characteristics of *C. indologenes* bacteremia and initial prompt antimicrobial treatments.

Key words: bacteremia, chryseobacterium indologenes, mortality

INTRODUCTION

Chryseobacterium indologenes, formerly *Flavobacterium indologenes*, is a yellow pigmented, filamentous, non-motile, oxidase-positive, indole-positive, and glucose-nonfermentative Gram- negative bacilli.[1] It is widely distributed in soil, water, plants, and foodstuffs. Contamination of distillate water has been reported to cause *C. indologenes infection*.[2]

C. indologenes was first described and isolated in 1983.[3] It was considered as colonization and without clinical significance[4] until 1996, when 12 cases of *C. indologenes* bacteremia were reported.[5] After that, several cases had been reported, and most of the patients were immunocompromised.[2,6-13] To the best of our knowledge, there are only six case series studies of *C. indologenes* bacteremia in the literature[1,5,14-17], and the largest one displayed 22 bacteremic episodes.[17]

Here, we investigated the incidence trend, clinical characteristics, and outcome of 48 episodes of *C. indologenes* bacteremia.

MATERIALS AND METHODS

Patients and definitions

The study was conducted at Tri-Service General Hospital, a 1700-bed medical center in Taipei, Taiwan. We retrospectively collected the data of patients with *C. indologenes* bacteremia from January 1, 2002 to April

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30, 2011. The protocol was approved by the TSGH Institutional Review Board (approval number: 2-101-05-074) with a waiver for informed consent.

Onset of bacteremia was defined as the date when positive blood culture was first obtained. Persistent bacteremia was defined as at least two or more consecutive positive blood cultures, at least 48 hours apart, during the same infectious episode. Nosocomial bacteremia was defined as the first positive blood culture obtained more than two days after admission. Community-acquired bacteremia was defined as a positive blood culture taken on or within 48 hours of admission. Healthcare-associated bacteremia was identified if any of the following criteria were present: more than 48 hours of hospitalization in the past 90 days, receipt of hemodialysis, receipt of intravenous medication or home wound care in the past 30 days, and residence in a nursing home or long-term care facility.[18]

Pneumonia was defined as new development of patchy opacity or *C. indologenes* yielded from the sputum culture collected at the day of bacteremic onset. Appropriate treatment was defined as antimicrobial agents administered were susceptible to antibiogram.

Microbiologic methods

Blood culture samples were processed by the BacT/AlerT blood culture system. Positive samples were examined by Gram stain and culture on CAN agar, MacConkey agar and chocolate agar for further identification. Antimicrobial susceptibilities of *C. indologenes* isolates collected between January 2002 and December 2006 were determined by the disk diffusion methods. VITEK 2 system with an AST GN-32 card was used to identify the minimal inhibitory concentrations (MICs) values for *C. indologenes* isolates collected after January 2007. The breakpoints of MICs for susceptibility were determined using the Clinical and Laboratory Standards Institute (CLSI) standards for susceptibility to non-fermentative gram-negative bacillus.[18]

Statistical analysis

Contingency data were analyzed using a two-tailed Chi-square test. Continuous data were compared using an independent-sample t-test. Variables with a two-tailed p value less than 0.05 were considered statistically significant. Logistic regression models were used to explore independent risk factors for 14-day mortality. Univariate analyses were performed separately for each of the risk factor variables to ascertain the odds ratio (OR) and 95% confidence interval (CI). All biologically plausible variables with a p value of ≤ 0.20 in the univariate analysis exhibited by at least 10% of the patients were considered for inclusion in the logistic regression model for multivariate analysis. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

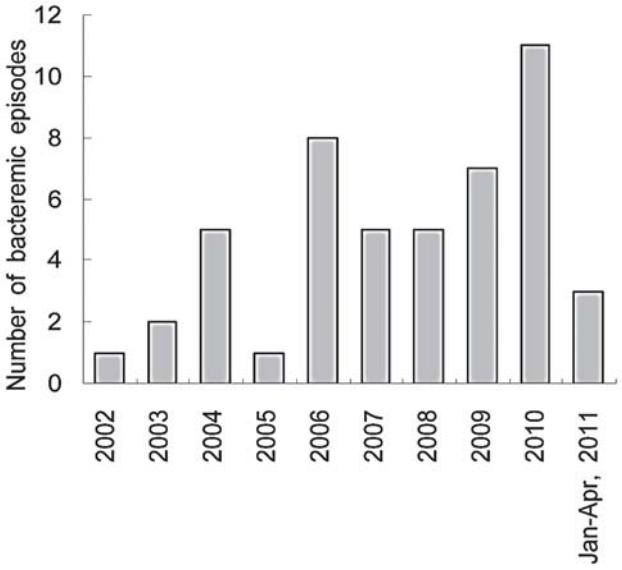

Fig. 1 Annual incidence of Chryseobacterium indologenes bacteremia at Tri-Service General Hospital, Taipei, Taiwan.

RESULTS

Forty-eight episodes of *C. indologenes* bacteremia in 47 patients were identified between January 1, 2002 and April 30, 2011. There was no outbreak of *C. indologenes* infection during the study period. The annual number of bacteremic episodes is shown in Figure 1, and an increasing trend of incidence of *C. indologenes* bacteremia is observed.

The only patient with recurrent bacteremia was a 93-year-old female receiving maintenance hemodialysis and long-term ventilator support. She had the first episode of bacteremia in July 2010 and the second episode of bacteremia nine months later. The first episode of bacteremia was secondary to pneumonia, and the second one was primary. The isolates of blood and sputum from her first bacteremia yielded *C. indologenes* with identical antibiograms.

The demographic data, comorbidity, and clinical characteristics of the 47 patients are summarized in Table 1 and 2.

Table 1 Demographics data and comorbidities of 47 patients with *Chryseobacterium indologenes* bacteremia

Variables	No. of patients, n (%)
Mal	29 (62)
Age, year (range)	69 (20-98)
Comorbidities	46 (98)
Cardiovascular system	26 (55)
Valvular heart disease	6 (13)
Respiratory system	18 (38)
Ventilator dependence	14 (30)
Chronic obstructive lung disease	6 (13)
Pulmonary tuberculosis	3 (6)
Bronchial asthma	2 (4)
Central nervous system	16 (34)
Cerebral infarction	10 (21)
Brainstem infarction	2 (4)
Intracranial hemorrhage	2 (4)
Malignancy	14 (30)
Head and neck cancer	5 (11)
Lung cancer	3 (6)
Lymphoma	3 (6)
Hepatoma	2 (4)
Skin and soft tissue	11 (23)
Decubitus ulcer	4 (9)
Necrotizing fasciitis	2 (4)
Burn injury	2 (4)
Diabetes	19 (40)
Uremia	9 (19)
Chronic renal failure	5 (11)
Cirrhosis of liver	5 (11)
Autoimmune disease	2 (4)

Table 2 Clinical characteristics and outcomes of 48 episodes of *Chryseobacterium indologenes* bacteremia

Variables	No. of episodes, n (%)
Acquisition of bacteremia	
Nosocomial	44 (92)
Healthcare-associated	3 (6)
Community-acquired	1 (2)
Onset day of nosocomial bacteremia (mean ± SD, days)	41±50
Hospital stay (mean ± SD, days)	73±65
Tunneled catheter	26 (54)
Location of bacteremia onset	
General wards	26 (54)
Intensive care units	22 (46)
Infection sources	
Primary bacteremia	33 (69)
Pneumonia	9 (19)
Catheter-related	4 (8)
Colitis	1 (2)
Cellulitis	1 (2)
Persistent bacteremia	5 (10)
Appropriate antibiotic treatment	19 (40)
Clinical outcome	
14-day mortality	8 (17)
In-hospital mortality	16 (33)

Most patients (46/47, 98%) had comorbidities. The only previous healthy patient was a 43-year-old female, who presented with fever, low abdominal pain and watery diarrhea after eating homemade jelly made from seaweed agar. Hypertension was the most common comorbidity (23/47, 49%), followed by diabetes mellitus (19/47, 40%). Eighteen patients (38%) had underlying respiratory diseases, and 14 (30%) of them were ventilator dependent. One-third of patients (16/47, 34%) had pre-existing neurologic disorders, such as infarction and hemorrhage. Head and neck cancers were the most common malignancy (5/47, 11%).

Almost all the bacteremic episodes (47/48, 98%) were nosocomial or healthcare-associated, and only one (2%) was community-acquired. The average number of days of bacteremia onset was 41 days after admission. The average length of hospitalization was 73 days. Among bacteremic sources, 33 episodes (69%) were primary bacteremia, followed by pneumonia (9/48, 19%) and catheter-related infection (4/48, 8%).

Only 19 patients (40%) received appropriate antimicrobial therapy. The 14-day and in-hospital mortality rates were 17% and 33%, respectively. Inappropriate antimicrobial therapy was not associated with higher 14-day and in-hospital mortality ($p = 0.451$ and 0.41, respectively).

The results of antibiotic susceptibility tests of the 48 isolates are shown in Table 3. All of the isolates were non-susceptible to first generation cephalosporins. Most isolates were non-susceptible to ampicillin, ceftriaxone, imipenem, aminoglycosides, ciprofloxacin, ceftazidime, and cefepime.

A summarized comparison of clinical characteristics between survivors and non-survivors is given in Table 4.

Table 3 Antimicrobial non-susceptiblity of 48 bacteremic strains of *Chryseobacterium indologenes*

Antimicrobial agents	No. (%) of non-susceptibility
Cefazolin/cephalothin	48/48 (100)
Ampicillin	47/48 (98)
Ceftriaxone	45/48 (94)
Gentamicin	45/48 (94)
Amikacin	42/48 (88)
Imipenem	41/48 (85)
Ciprofloxacin	32/48 (67)
Ceftazidime	30/48 (63)
Cefepime	27/48 (56)
Trimethoprim-sulfamethoxazole	3/13 (23)
Flomoxef	3/15 (20)

Table 4 Clinical characteristics between survivors and non-survivors in 48 episodes of *Chryseobacterium indologenes* bacteremia*

Variables	Non-survivors, n=16	Survivors, n=32	*p* value
Male gender	11	18	0.41
Age >70 years	10	17	0.55
Malignancy	4	7	0.81
Ventilator dependence	6	9	0.52
Intensive care unit admission	9	13	0.32
Tunneled catheter	12	14	0.04
Infective source			
Pneumonia	5	4	0.12
Primary bacteremia	11	22	1.0
Onset of bacteremia >50 days after admission	6	4	0.045
Persistent bacteremia	3	2	0.19
Antimicrobial non-susceptibility			
Amikacin	16	26	0.07
Ceftazidime	14	16	0.01
Cefepime	12	14	0.04
Imipenem	16	26	0.07
Ciprofloxacin	12	20	0.40
Inappropriate antimicrobial therapy	5	14	0.41

*Using in-hospital mortality.

Patients with tunneled catheter, prolonged onset of bacteremia after admission, and bacteremia caused by isolates which were non-susceptible to ceftazidime or cefepime had a higher risk of mortality.

Following logistic regression analysis, no factor was associated with 14-day mortality. Pneumonia (OR = 31.359; 95% CI = 1.35-729.39; $p = 0.032$) and non-susceptibility to ceftazidime (OR = 21.057; 95% CI = 2.28-194.57; $p = 0.007$) were independent risk factors for in-hospital mortality.

DISCUSSION

To the best of our knowledge, there are limited studies on *C. indologenes* bacteremia[1,5,14-17], with the most extensive one investigating 22 bacteremic episodes within 7 years.[17] Our study that enrolled 48 bacteremic episodes is currently the largest. According to our investigation, *C. indologenes* bacteremia was usually nosocomial acquired in elder patients with various comorbidities, and the mortality was high. Potential risks for mortality included: tunneled catheter insertion, prolonged onset of bacteremia, and infective strains that were non-susceptible to ceftazidime or cefepime.

Increasing incidence of *C. indologenes* bacteremia is observed (Figure 1), which is concordant with a recent study reporting the incidence of *C. indologenes* bacteremia increased gradually after 2006 and correlated with increasing consumption of colistin and tigecycline.[17]

In this study, we identified five episodes of persistent bacteremia, and one patient had two episodes of bacteremia within a nine-month interval. Recurrent bacteremia was reported in a cancer patient who had his second episode of bacteremia six days after completing antimicrobial treatment.[7] However, the persistence and recurrence of *C. indologenes* bacteremia were not associated with higher mortality in our study.

Community-acquired *C. indologenes* bacteremia has been reported in a previously healthy infant and a male adult.[5,13] In the current study, there was one patient with community-acquired bacteremic colitis caused by contaminated foods. Contaminated water has been identified as a cause of *C. indologenes* bacteremia.[2] Though large scale of outbreak of *C. indologenes* has never been reported, it is still a potential pathogen in community and nosocomial settings.

Bacteremic cellulitis caused by *C. indologenes* has also been reported previously[6], and burn patients seemed to be prone to *C. indologenes* bacteremia.[5,14,15] In our patients, skin defects such as burns, surgical wounds, and decubitus ulcers, were also found to be the sources of *C. indologenes* bacteremia. Besides, skin defects as a portal

of *C. indologenes* bacteremia was also found in our patients with head or neck tumors and in a previous report.[9]

C. indologenes is known to exhibit extensive resistance to penicillins, cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones.[5] It has been reported the resistance is caused by extended-spectrum β-lactamase.[19] Our isolates of *C. indologenes* also exhibited extensive resistance toward various classes of antimicrobial agents except flomoxef. It might therefore be a potential therapeutic option treating *C. indologenes* infections. However, identifying the efficacy requires further investigation.

Based on the current study, pneumonia and isolates non-susceptible to ceftazidime were independent risk factors of in-hospital mortality. Inappropriate antimicrobial therapy was not associated with higher 14-day and in-hospital mortality in our patients. Our findings revealed the outcome of *C. indologenes* bacteremia was not principally influenced by the antibiotic itself. Besides, the virulence and pathogenicity of *C. indologenes* might be low. Further, underlying diseases and other associated clinical condition may determine the prognosis. Even so, we still suggest prompt antimicrobial use may have a role in treating such patients, especially in those with the underlying condition mentioned above. Chen *et al*. showed potential antimicrobial choices for *C. indologenes* infections may include trimethoprim-sulfamethoxazole(TMP-SMZ) and cefoperazone-sulbactam.[17] According to our results, flomoxef and TMP-SMZ are potentially therapeutic choices. However, further investigations are required to prove the validity of these agents.

Our study has several limitations. First, it is a retrospective study, missing data or non-documented records may hide potential risk factors. Second, the pathogenicity and virulence factors of *C indologenes* remain unclear. Third, our case number is limited in that further analyses cannot be achieved, such as antimicrobial treatment comparisons. A well-designed prospective study will be necessary to overcome these limitations.

In conclusion, the emergence of *C. indologenes* bacteremia has had a great clinical impact on inpatient care. For prompt treatment, it is important to identify the clinical characteristics of *C. indologenes* bacteremia including primary and pulmonary origins, prolonged hospitalization, tunnel catheter insertions, and extensive antimicrobial resistances.

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DISCLOSURE

The authors declared this study has no conflicts of interest.

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