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Clinical characteristics and risk factors for mortality in adult patients with persistent candidemia

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Summary *Background:* We investigated the clinical characteristics and risk factors for mortality in adults with persistent candidemia.
Methods: All patients ≥18 years old with candidemia in two Korean tertiary hospitals from 2007 to 2014 were investigated. Persistent candidemia was defined as isolation of the same *Candida* species ≥5 days after initiation of antifungal therapy. Non-persistent candidemia was defined as candidemia persisting for ≤3 days after initiation of antifungal therapy.
Results: Candida tropicalis (29.2%) was the most common pathogen in persistent candidemia, and *Candida albicans* (35.9%) was the most common in non-persistent candidemia. Central venous catheter (CVC) (OR, 1.99; 95% CI, 1.05–3.78; $P = 0.034$), longer hospital stay (OR 1.01; 95% CI, 1.01–1.02; $P = 0.025$), and severe sepsis (OR 2.25; 95% CI, 1.11–4.56; $P = 0.024$) were independent risk factors for persistent candidemia. *C. tropicalis* was independently related to 30-day mortality (OR, 4.12; 95% CI, 1.27–13.36; $P = 0.018$), together with septic shock (OR, 5.81; 95% CI, 1.32–24.70; $P = 0.017$) and use of a corticosteroids (OR, 5.31; 95% CI, 1.07–26.29; $P = 0.041$) in persistent candidemia.
Conclusion: C. tropicalis is the predominant pathogen and cause of death in patients with persistent candidemia.

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Introduction

Persistent fungemia is an increasingly recognized complication of candidemia, and it has been reported in 8—15% of candidemia patients in prospective studies.[1] Several studies have described either the clinical characteristics or risk factors of persistent candidemia and predictors of mortality in these patients.[2—6] Chen et al.[6] reported that persistent candidemia was associated with CVC-related infection and underlying disease status in patients with hematological malignancies. In addition to host factors, drug resistance, low serum levels of drugs, endovascular infection, deep-tissue abscesses, and infections associated with prosthetic materials have been reported to be risk factors for persistent candidemia.[1,7] However, as the definition of persistent candidemia and the population of patients with candidemia were discordant among these studies, the meanings of their findings are unclear. Furthermore, unlike bacteremia, in which persistent positive blood cultures after the initiation of antibacterial therapy indicate a worse clinical outcome, whether persistent candidemia has similar clinical significance is unclear.[2—4,6] While some studies have shown that persistent candidemia is associated with worse outcomes, such as treatment failure,[8] metastatic complications,[5] and increased risk of death,[9] others have found no such association.[2,6] Furthermore, as most studies of persistent candidemia have been conducted in neonates, there is difficulty generalizing the findings to adult patients. Therefore, this study was performed to determine the risk factors, clinical significance and predictors of mortality in adult patients with persistent candidemia compared to those with non-persistent candidemia.

Patients and methods

Patient selection

All patients $\geq$18 years old who presented to two tertiary hospitals (Chonnam National University Hospital, 1000 beds, Gwang-ju, Republic of Korea; and Chonnam National University Hwasun Hospital, 700 beds, Hwasun, Republic of Korea) with candidemia from 2007 to 2014 were investigated. Only the first episode of candidemia in a patient was included. Demographic and clinical data were collected by reviewing the electronic medical records of the patients. The Institutional Review Boards of the two participating hospitals approved this study.

Definition

Candidemia was diagnosed in patients with at least one blood culture positive for *Candida* species. Persistent candidemia was defined as isolation of the same *Candida* species $\geq$5 days after initiation of antifungal therapy. Non-persistent candidemia was defined as candidemia persisting for $\leq$3 days after initiation of antifungal therapy.[4,10] Neutropenia was defined as an absolute neutrophil count of $<$500 cells/mm^3. Cardiac disease included symptomatic heart failure with or without valvular dysfunction. Chronic kidney disease was defined as reduced glomerular filtration rate $<$60 mL/min/1.73 m^2 for more than 3 months.[11] Central venous catheter (CVC)-related infection was defined as isolation of a microorganism from the bloodstream of a patient who had concurrent clinical manifestations of sepsis and no other source of candidemia other than the catheter.[6] As a source of candidemia, intra-abdominal infection included gastrointestinal tract infections, which was considered the source of candidemia if patients had signs or symptoms related to the gastrointestinal tract prior to the onset of candidemia and did not have any other source, using a previously reported definition with minor modifications.[8,12] Dissemination of candidemia was defined if one or more of the following were present: chorioretinitis or endophthalmitis diagnosed by an ophthalmologist via fundoscopic examination; endocarditis with echocardiographic evidence of valvular vegetation; or solid organ involvement with focal, discrete, or nodular lesions on computed tomography (CT), magnetic resonance imaging, or ultrasound scan other than the primary lesion.[13] Severe sepsis was defined as sepsis-induced tissue hypoperfusion or organ dysfunction, as manifested by one of the following: sepsis-induced hypotension (systolic arterial pressure $<$90 mm Hg, a mean arterial blood pressure $<$65 mm Hg, or a reduction in systolic blood pressure of $<$40 mm Hg from baseline); lactate above the upper limits of normal ($>$2 mmol/L); urine output $<$0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation; acute lung injury with PaO_2/FiO_2 $<$300 mm Hg; creatinine $>$2.0 mg/dL; bilirubin $>$2 mg/dL; platelet count $<$100,000 cells/μL; or coagulopathy (international normalized ratio $>$1.5 or aPTT $>$60 s). Septic shock was defined as severe sepsis plus hypotension that could not be reversed by fluid resuscitation.[14] Antifungal treatment was considered inappropriate if the *Candida* blood isolate was resistant to the initially administrated antifungal agent.

Microbiological test

Candida species were identified and antifungal susceptibility was determined using the Vitek 2 automated system (bioMérieux, Marcy L'Etoile, France).

Statistical analyses

Categorical variables were compared using Fisher's exact test or the Pearson χ^2 test as appropriate, and continuous variables were compared using Student's *t*-test. Multivariate analyses were performed using the Cox-regression hazard model in a backward stepwise conditional manner. Variables with $P < 0.10$ in univariate analysis were candidates for multivariate analysis. Odds ratios (ORs) and 95% confidential intervals (CIs) were calculated. The subjects were stratified as persistent and non-persistent to investigate the differences in mortality risk factors. All tests of significance were two-tailed, and P values ≤ 0.05 were deemed to indicate statistical significance. Statistical analyses of the data were performed using the PASW statistics software (version 18.0; SPSS Inc., Chicago, IL).