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Epidemiology, microbiology, clinical characteristics, and outcomes of candidemia in internal medicine wards—a retrospective study

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SUMMARY

Background: The clinical characteristics of internal medicine ward (IMW) patients with candidemia are unclear. The aim of this study was to define the clinical characteristics of candidemic IMW patients and to study the incidence, species distribution, and outcomes of these patients compared to surgical and intensive care unit (ICU) candidemic patients.

Methods: A retrospective cohort of candidemic patients in IMWs, general surgery wards, and an ICU at Beilinson Hospital during the period 2007–2014 was analyzed.

Results: A total of 118 patients with candidemia were identified in six IMWs, two general surgery wards, and one ICU in the hospital. *Candida albicans* was the leading causative agent (41.1%). Higher proportions of *Candida parapsilosis* and *Candida tropicalis* isolates were observed in the IMW patients. IMW patients were significantly older, with poorer functional capacity, and had more frequently been exposed to antibiotic therapy within 90 days, in particular β-lactam–β-lactamase inhibitor combinations and cephalosporins. At onset of candidemia, a significantly lower number of IMW patients were mechanically ventilated ($p < 0.01$); these patients did not have central line catheters comparable to ICU and surgical patients ($p < 0.001$). They were less likely to receive adequate antifungal therapy within 48 h, and this was the only significant predictor of survival in these patients ($p = 0.028$): hazard ratio 3.7 (95% confidence interval 1.14–12.5) for therapy delayed to >48 h.

Conclusions: IMW candidemic patients account for a substantial proportion of candidemia cases and have unique characteristics and high mortality rates.

1. Introduction

Invasive candidiasis is the most common fungal infection among hospitalized patients. Epidemiological studies over the past decade have identified *Candida* species as the fourth most common cause of nosocomial bloodstream infection (BSI), although these reports were mainly for critical care units.[1] Despite the advances in antifungal therapy, candidemia continues to contribute to greater mortality, prolonged hospitalization, and increased costs of care.[2,3] Candidemia has been studied extensively worldwide.[3–8] It has been well described in specific populations, including surgical patients, intensive care unit (ICU) patients, mechanically ventilated patients, and those with central venous catheters (CVC), indwelling urinary catheters, and exposure to total parenteral nutrition (TPN).[4,5,9,10] Data on candidemia in non-surgical, non-ICU patients remain scarce. The diagnosis of candidemia in internal medicine wards (IMWs) is often delayed or overlooked, and consequently these patients have worse outcomes compared to candidemic surgical or ICU patients.

A shift in etiology of candidemia has been reported over the past 10 years. While *Candida albicans* is still considered the most common species causing candidemia, increasing rates of *Candida tropicalis*, *Candida parapsilosis*, *Candida glabrata*, and *Candida krusei* in candidemia have been reported worldwide.[5,11–14] Candidemia rates and the distribution of *Candida* species vary geographically.

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Therefore, there is a need to monitor the trends in incidence, species distribution, and antifungal drug susceptibility profiles in every country.[6–8,12,15–20] The primary objective of this study was to evaluate the clinical characteristics of candidemia in patients admitted to IMWs compared to patients in surgical wards and the ICU. Secondary objectives were to evaluate the incidence of candidemia among IMW patients compared to surgical and ICU patients, to identify the species distribution and antifungal susceptibility patterns over the years, and to evaluate in-hospital and overall mortality rates.

2. Materials and methods

2.1. Subjects and study design

All consecutive candidemic adult patients (>18 years) hospitalized in six IMWs, two surgical wards, and one ICU, diagnosed between January 2007 and December 2014, were included in this retrospective observational study. The study was conducted at Rabin Medical Center, Beilinson Hospital in Petah Tikva, Israel. This is a 900-bed primary and tertiary care, university-affiliated hospital that serves an urban, elderly population of about 400 000 as a first-line facility. It is also a referral center for several hospitals in the vicinity. The hospital has four main ICUs and also small ICUs in which patients undergo mechanical ventilation within the six IMWs and two surgical departments. Data regarding demographic and clinical characteristics, treatment, and clinical outcomes were collected from the patient medical records.

Adequate antifungal treatment was considered when the Candida isolate was susceptible to the administered antifungal therapy and treatment started within 48 h from the first blood culture performed.[4] Finally, a comparison was made of all dependent variables between candidemic patients in the IMWs, general surgery wards, and ICU.

2.2. Microbiological methods

The diagnosis of candidemia was defined as the growth of *Candida* species in one or more blood cultures in a patient with temporally related clinical signs and symptoms of infection. Each patient was included once; only the first episode of candidemia was included for each patient. Isolates were detected in blood cultures using several tests, including CHROMagar Candida and the germ tube assay for all suspected *C. albicans* isolates, VITEK II, and the API ID 32 C (bioMérieux, Marcy l'Etoile, France). The in vitro activity of the antifungal agents was measured using the Etest (AB Biodisk, Solna, Sweden) in accordance with the manufacturer's instructions (Appendix 1).

2.3. Statistical analysis

The incidence of candidemia was calculated per 1000 hospital admissions, and 95% confidence intervals (CI) were estimated assuming a Poisson distribution of cases. The distribution of *Candida* species was analyzed according to the study period and hospital ward. All dichotomous variables, expressed as the number and percentage, were compared by Chi-square test (for more than two groups) or Fisher's exact test (for two groups). Continuous variables, expressed as the mean ± standard deviation or as the median and interquartile range (IQR, 25^{th}–75^{th} percentiles), were compared using analysis of variance (ANOVA). Variables found to be statistically significant in the descriptive analysis and/or those with clinical relevance based on previous studies showing the importance of these covariates on mortality were analyzed according to 30-day mortality.[4] A planned multivariable analysis was conducted for variables found to be statistically significant in the univariate analysis. Results were expressed as hazard ratios (HR) and 95% CI. Statistical significance was established using a probability level of 5% ($p < 0.05$). The statistical analysis was performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

A total of 106 consecutive patients with candidemia were identified during the study period; 51 patients were hospitalized in the six IMWs, 31 in the two surgical departments, and 24 patients in the ICU.

3.1. Epidemiology

The overall incidence rate was 0.61 episodes/1000 hospital admissions (range 0.42–0.92/1000 hospital admissions, 95% CI 0.5–0.7). The incidence rate according to hospital ward was 0.34 episodes/1000 hospital admissions (95% CI 0.2–0.5) in the IMWs, 0.82 episodes/1000 hospital admissions (95% CI 0.5–1.1) in the surgery wards, and 7.35 episodes/1000 hospital admissions (95% CI 4.9–9.8) in the ICU. These incidence rates are comparable with previously published data in Israel.[9]

During the study period, *C. albicans* was the leading causative agent of candidemia (52 patients, 41.1%), followed by *C. glabrata* (28 patients, 23.7%), *C. parapsilosis* (18 patients, 15.2%), and *C. tropicalis* (16 patients, 13.6%); other *Candida* species included *C. krusei* in the ICU, *Candida lusitaniae*, *Candida lipolytica*, and *Candida rugosa* (one isolate of each, in four (7.6%) patients) (Fig. 1A). There was a higher proportion of *C. glabrata* isolates in patients hospitalized in the surgery wards and ICU (Fig. 1B), while there were higher proportions of *C. parapsilosis* and *C. tropicalis* isolates in the IMW patients. No significant difference in the proportion of *C. albicans* between the IMW patients and the ICU and surgery ward patients was found (Fig. 1C). Over the years, the percentage of *C. albicans* decreased from 53.8% to 35.3% and the percentage of *C. glabrata* increased from 7.7% to 29.4%. Trends in the proportions of other isolates could not be demonstrated.

3.2. Baseline and clinical characteristics

Patient baseline and clinical characteristics were available for 106 of the 118 patients. These characteristics are summarized in Tables 1 and 2. Comparing candidemic patients in the IMWs with those in the surgery wards and ICU, IMW patients were significantly older: mean age 75 ± 11.7 years vs. 65.9 ± 15.8 and 57.7 ± 16.4 years in the surgery wards and ICU, respectively ($p < 0.0001$). The median age was 76 (IQR 47–95) years in the IMWs, 67 (IQR 19–95) years in the surgery wards, and 62.5 (IQR 20–81) years in the ICU.

IMW patients had poorer functional capacity, were more commonly admitted from a nursing home, and had more frequently been exposed to antibiotic therapy within 90 days, in particular β-lactam–β-lactamase inhibitor combinations and cephalosporins. The mean Charlson score of IMW patients was 4.4 ± 2.3, which was significantly higher than the mean score of surgery ward patients (3.1 ± 2) and ICU patients (3 ± 2) ($p < 0.006$). The median Charlson score was 4 (IQR 0–11) in the IMW patients, 2 (IQR 0–8) in the surgery ward patients, and 3 (IQR 0–6) in the ICU patients.

As expected, previous abdominal surgery and parenteral nutrition were significantly more frequent in surgery ward and ICU patients. At the onset of candidemia, a significantly lower number of IMW patients were mechanically ventilated ($p < 0.01$); these patients did not have central line catheters comparable to ICU and surgical patients ($p < 0.001$) and had significantly more thrombocytopenia than surgical patients ($p < 0.01$). Interestingly,