Epidemiology of Candidemia – A Nationwide Survey in Israel

G. Rennert, H.S. Rennert, S. Pitlik, R. Finkelstein, R. Kitzes-Cohen

Summary

Bloodstream infections with *Candida* are often lethal and have been reported to be increasing in frequency. The current retrospective study describes the magnitude and epidemiological characteristics of candidemia in all western-type hospital facilities in Israel in 1994. Comprehensiveness of the data from the reporting hospitals was checked by cross-study of the data from the infectious diseases records and from the hospitalization records. Vital status of all reported cases was evaluated 1 year after the diagnosis. Data on 298 newly diagnosed cases of candidemia were received from 14 of the 18 general hospitals in Israel. The proportion of candidemia in the Israeli hospitals ranged from 0.1 to 0.01% of all admissions, with a mean of 0.05%. The incidence of candidemia differed significantly between the wards from 4–5/10,000 in general surgery and internal medicine wards to about 60/10,000 and 80/10,000 in intensive care and preterm units, respectively. Of all detected cases 53.6% were *Candida albicans*. Another nine specific species of *Candida* (mainly *Candida parapsilosis*, *Candida tropicalis* and *Candida glabrata*) were detected, with major differences between the various hospitals. The species of *Candida* differed significantly by sex and age. Of the cases of candidemia 21.5% died within 30 days of the isolation of the pathogen. The one-year mortality rate was 31.9%. Species-specific 30-day mortality rate was highest for *C. glabrata*. Throughout the analysis, *C. glabrata* emerged as a unique cause of candidemia, producing higher mortality, appearing at a younger age and predominating among females.

Key Words

Candida · Epidemiology · Israel

Infection 2000;28:26–29

Introduction

Bloodstream infections with *Candida* have been reported in various medical settings to be increasing in frequency among hospitalized patients [1–8]. A recent report from the US revealed that *Candida* was the fourth leading cause of nosocomial bloodstream infection, accounting for 8% of all infections [9].

This is not surprising if one takes into account the dramatic increase in hospitalizations of immunocompromized and elderly patients and the rise in treatments leading to immunosuppression, which is considered to be the major risk factor for candidemia [10–14].

The epidemiology of candidemia has changed over the past decade, with a strong shift from *Candida albicans* to the various *Candida* species.

These infections frequently have high mortality rates and are associated with significant financial expense for treatment and hospitalization days [15, 16]. It is thus important to better understand the new situation, study the local characteristics of these infections, and make the professional teams aware of them to achieve a better medical outcome.

The current retrospective study was carried out to evaluate the magnitude and epidemiological characteristics of candidemia in the western-type hospital facilities in Israel.

Patients and Methods

All 18 hospital-based infectious disease units in Israel were asked to report to the study center all cases of blood-culture proven *Candida* infections during 1994.

The units were requested to provide demographic, administrative and laboratory information. Types of treatment and background diseases were available only for a minority of the cases.

G. Rennert *(corresponding author)*, **Hedy S. Rennert**
Dept. of Community Medicine and Epidemiology, Carmel Medical Center and Technion Faculty of Medicine, IL-34362 Haifa, Israel;
Phone: +972-4-8250474, Fax: +972-4-8344358
S. Pitlik
Infectious Diseases Unit, Beilinson (Rabin) Medical Center, Petah-Tikva, Israel
R. Finkelstein
Infectious Diseases Unit, Rambam Medical Center, Haifa, Israel
R. Kitzes-Cohen
Infectious Diseases and Clinical Pharmacology Unit, Carmel Medical Center and Technion Faculty of Medicine, Haifa, Israel

Received: January 14, 1999 • Revision accepted: December 4, 1999

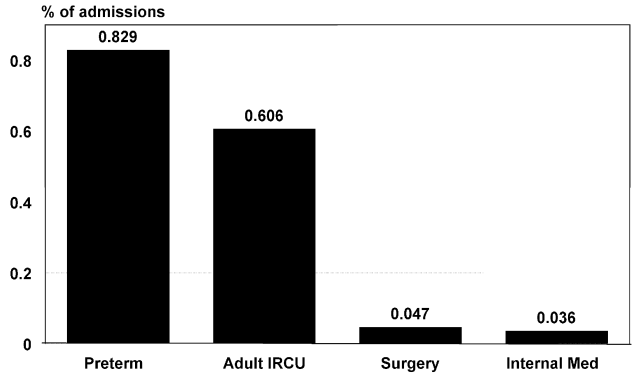
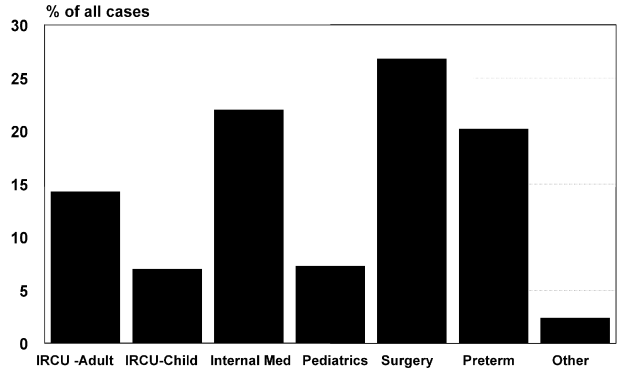


Figure 1
Candidemia incidence by type of ward, Israel 1994.



Based on 287 cases in 14 hospitals.

Figure 2
Distribution of candidemia cases by hospital ward, Israel 1994.

The demographic information included age and sex. The administrative data included the ward(s) of hospitalization, and the dates of admission and discharge. Laboratory data included the species of *Candida* isolated, and the number and dates of isolations.

Comprehensiveness of the data from the reporting hospitals was achieved by extracting the data from the infectious diseases records and the microbiology laboratories. In some hospitals records were also checked against computerized hospitalization records but no additional cases were detected. Discharge letters were sought in a sample of 53 cases.

Vital status of all reported cases was evaluated 1 year after the diagnosis of candidemia for each patient, and the date of death, if relevant, was recorded. This was done using the National Israeli Population Register.

Results

Adequate data on 298 newly diagnosed cases of candidemia were received from 14 of the 18 general hospitals in Israel, among them all but one of the major medical centers in Israel. In this latter medical center, 39 cases were diagnosed and reported, but were not included in the detailed analysis due to lack of specific information.

Incidence Rate

The overall incidence of candidemia in our series was 4.33/10,000 hospitalizations. This incidence differed significantly between the various hospitalizing wards from 4–5/10,000 in general surgery and internal medicine wards to about 60/10,000 and 80/10,000 in intensive care and preterm units, respectively (Figure 1). Because of the higher number of hospitalizations in the general surgery and internal medicine wards, however, most of the cases of candidemia (51%) are diagnosed in these low-incidence wards (Figure 2).

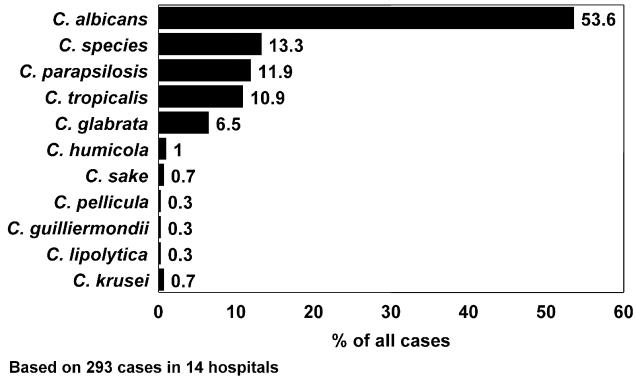
In 27 (60%) of the 45 adult sample cases for which clinical data were made available, septicemia was diagnosed after surgery (11 cases in the gastrointestinal tract, seven cases after cardiac surgery), another seven (16%) cases were on dialysis treatment, and another six (13%) were admitted to the hospital with pyrexia as a presenting symptom.

The proportion of candidemia in the Israeli hospitals ranged from 0.1 to 0.01% of all admissions, with a mean of 0.05%.

The majority of the detected cases was men (62%), and over the age of 50 (51.1%).

Species of *Candida*

The most common *Candida* type detected in our series of patients was *C. albicans*, comprising 53.6% of all cases. Another nine specific species of *Candida* (mainly *Candida parapsilosis*, *Candida tropicalis* and *Candida glabrata*) and



Based on 293 cases in 14 hospitals

Figure 3
Distribution of candidemia cases by species of pathogen, Israel 1994.

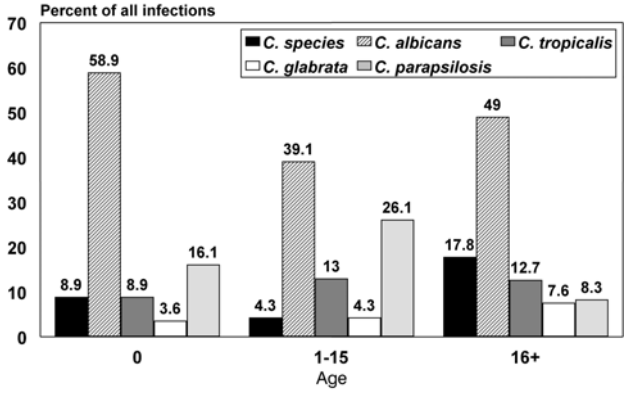


Figure 4
***Candida* species by age, Israel 1994.**

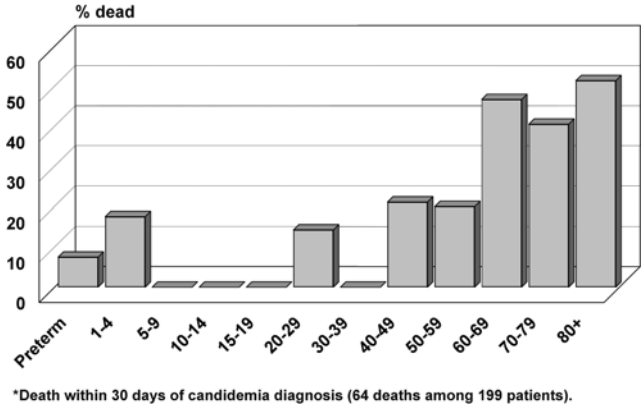


Figure 5
30-day mortality* for patients with candidemia, by age, Israel 1994.

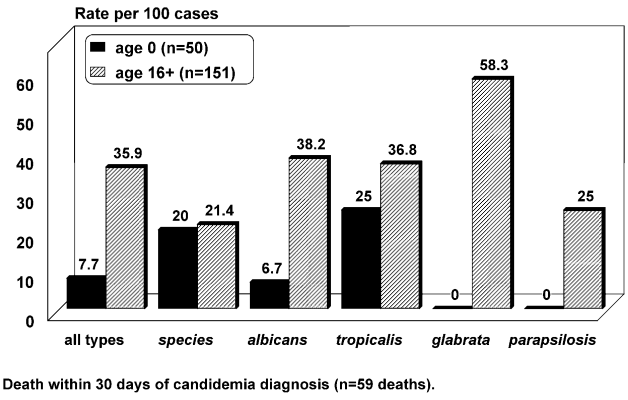


Figure 6
30-day mortality* from *Candida* species by age group, Israel 1994.

a large group of other undefined *Candida* species were detected (Figure 3). There were major differences in the internal distribution of the species of *Candida* isolated in the various hospitals. *C. albicans*, for example, ranged from 100% of the cases in one hospital to less than 30% in another.

The species of *Candida* differed significantly by sex, and were much lower in women for each of the *Candida* species except for *C. glabrata*. There was also a major difference in species of *Candida* by age (Figure 4).

Mortality Rate

64 of the 298 reported cases of candidemia (21.5%) died within 30 days of the isolation of the pathogen. The 1-year mortality rate was 31.9% of which 90% died within 90 days from the candidemia identification. The 30-day mortality was much higher for patients above 60 years of age than for any other age-group. The 30-day mortality among preterm babies was relatively low (Figure 5).

The overall 30-day mortality rate among adult patients was 42%. Species-specific 30-day mortality rate was highest for *C. glabrata*, and lowest for *C. parapsilosis* and other *Candida* species (Figure 6).

Throughout the analysis, *C. glabrata* emerged as a unique cause of candidemia, producing higher mortality, appearing at a younger age and predominating among females (Figure 7).

Discussion

This study describes the incidence of candidemia during hospitalization in Israel. From the data presented in this study, candidemia emerges as an infrequent but highly lethal infection.

Data provided in this analysis came from reports of all participating hospitals. These include different types of hospitals, some of which have major oncology and transplantation facilities and all of which have intensive care units and preterm newborn wards. Of the four hospitals not included in this analysis, three are small local hospitals and one is a large tertiary hospital from which only the total number of cases, by species of *Candida*, was transferred. It does not seem plausible that this lack of data has significantly changed the results and conclusions. The overall incidence rates found in this study are in line with those described by the CDC and others [17, 7]. The mortality rates in this study, though high, are somewhat lower than those described by some authors [4, 11, 17] but not by others such as *Karlowsky* et al. (23% in a tertiary hospital) [18]. Mortality in ICU was reported to be higher (58%), but only about 20% was attributed to the *Candida* infection itself [7]. It is, however, hard to compare mortality figures between institutes as they depend heavily on the case-mix of patients. The main possible explanation for the difference is in the case-mix involved in the study. *Way's* analysis [11], for example, includes only 8% preterm babies (who are at a lesser risk of death) versus about 25% preterm babies in our series.

The distribution of species of *Candida* in this study was somewhat different from that described by *Fraser* et al. [3] in a tertiary hospital, with more *C. parapsilosis* and less *C.*

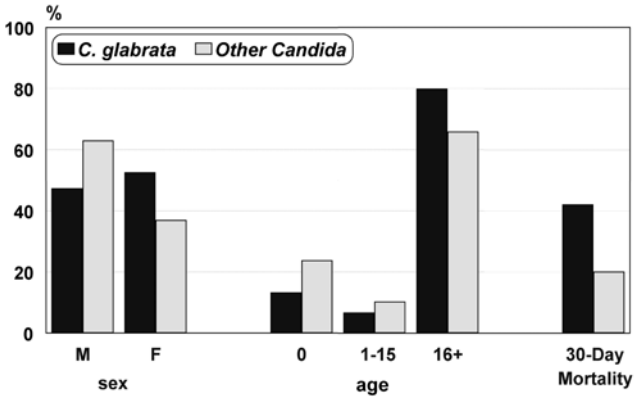


Figure 7
***C. glabrata* vs other candidemias, Israel 1994.**

albicans, *C. tropicalis* and *C. glabrata* in our data. *C. albicans* was reported to be responsible for 52–53% of the candidemias in the current national registries in the US (SCOPE Program, SENTRY Program) [9, 19], similar to the Israeli figure and significantly different from the US figures some 15 years ago [2]. In a Canadian report for 1992–1994 *C. albicans* was still responsible for almost 70% of the candidemias [16]. *C. parapsilosis*, found to be the second leading *Candida* species in children and infants in our series, was found to be the leading such pathogen in a report from a children's hospital in the US [20]. *Fraser's* data do not include any *Candida* species, which comprise more than 13% of our series. This possibly more prudent laboratory effort, in addition to the different medical setup might explain the differences. Another possibility is that due to the change in the patients' profile and treatments in recent years, new species or a new distribution of the pathogens are emerging.

The high mortality rate from *C. glabrata* has been formerly described by *Fraser* et al. [3] and *Komshian* et al. [4], but our analysis has yielded a higher mortality rate than that previously described, along with other as yet unreported characteristics of this pathogen. This is of major importance given the reports from the US, in which *C. glabrata* was found to be the most common non-*C. albicans* species [19].

This is the first report of its kind from Israel. As medical delivery patterns in Israel are considered "western", the results of this study can be generally applied to all medical setups of a mixture of secondary and tertiary facilities typical for a country or a state.

With the evolving increase in the number of medically or therapeutically immunosuppressed patients, medical teams can expect an increase in the diagnosis of these formerly rare pathogens. Since blood-borne candidemias are highly lethal, these medical teams need to become aware and knowledgeable about these diseases and closely follow up any change in the epidemiological patterns of the disease.

Acknowledgments

We would like to thank the following chiefs of infectious disease units in Israel for contributing data to this study: Dr. J. Karpuch, Asaf Harofe Hospital; Dr. I. Potesman, Bnei Zion Hospital; Dr. M. Shapira, Hadassah Medical Center; Dr. R. Raz, Haemek Hospital; Dr. C. Rudnicki, Hasharon (Golda) Hospital; Dr. Z. Landau, Kaplan Hospital; Dr. S. Lefler, Naharia Hospital; Dr. A. Yinnon, Share Zedek Medical Center; Dr. E. Rubinstein, Shiba Medical Center; Dr. F. Schlaeffer, Soroka Medical Center; Dr. S. Berger, Tel Aviv Municipal (Ichilov) Medical Center; Dr. Y. Igra, Tel Aviv Municipal (Ichilov) Medical Center; Dr. M. Dan, Wolfson Hospital.

References

1. Debusk CH, Daoud R, Thirumoorthi MC, Wilson FM, Khatib R: Candidemia: current epidemiologic characteristics and long-term follow-up of the survivors. Scand J Infect Dis 1994; 26: 697–703.
2. Beck-Sague CM, Jarvis WR: Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. J Infect Dis 1993; 167: 1247–1251.
3. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dungan WC: Candidemia in a tertiary hospital: epidemiology, risk factors and predictors of mortality. Clin Infect Dis 1992; 15: 414–421.
4. Komshian SV, Uwaydah AK, Sobel JD, Crane LR: Fungemia caused by *Candida* species and *Torulopsis glabrata* in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 1989; 2: 379–390.
5. Prasad JK, Feller I, Thomson PD: A ten-year review of *Candida* sepsis and mortality in burn patients. Surgery 1987; 102: 213–216.
6. Wright WL, Wenzel RP: Nosocomial *Candida*, epidemiology, transmission and prevention. Infect Dis Clin North Am 1997; 11: 411–425.
7. Voss A, Le Noble JLML, Verduyn Lunel FM, Foudraine NA, Meis JFGM: Candidemia in intensive care unit patients: risk factors for mortality. Infection 1997; 25: 10–12.
8. Lewis RE, Klepser ME: The changing face of nosocomial candidemia: epidemiology, resistance and drug therapy. Am J Health Syst Pharm 1999; 56: 525–533.
9. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP: National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE program. Diagn Microbiol Infect Dis 1998; 31: 327–332.
10. Way SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP: Hospital-acquired candidemia. The attributable mortality and excess length of stay. Arch Intern Med 1988; 148: 2642–2645.
11. Way SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP: Risk factors for hospital-acquired candidemia. A matched case-control study. Arch Intern Med 1989; 149: 2349–2353.
12. Miller PJ, Wenzel RP: Etiologic organisms as independent predictors of death and morbidity associated with bloodstream infections. J Infect Dis 1987; 156: 471–477.
13. Young RC, Bennet JE, Geelhoed GW, Levine AS: Fungemia with compromised host resistance. Ann Intern Med 1974; 80: 605–612.
14. Meunier F, Aoun M, Bitar N: Candidemia in immunocompromised patients. Clin Infect Dis 1992; 14 (suppl 1): S120–S125.
15. Rentz AM, Halpern MT, Bowden R: The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. Clin Infect Dis 1998; 27: 781–788.
16. Yamamura DI, Rotstein C, Nicolle LE, Loannou S: Candidemia at selected Canadian sites: results from the Fungal Disease Registry, 1992–1994. Fungal Diseases Registry of the Canadian Infectious Disease Society. Can Med Assoc J 1999; 160: 493–499.
17. Wenzel RP, Pfaller MA: *Candida* species: emerging hospital bloodstream pathogens. Infect Control Hosp Epidemiol 1991; 12: 524–525.
18. Karlowsky JA, Zhanel GG, Klym KA, Hoban DJ, Kabani AM: Candidemia in a Canadian tertiary hospital from 1976–1996. Diagn Microbiol Infect Dis 1997; 29: 5–9.
19. Pfaller MA, Jones RN, Doern GV, Sader HS, Hollis RJ, Messer SA: International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada, and South America for the SENTRY Program. The SENTRY Participant Group. J Clin Microbiol 1998; 36: 1886–1889.
20. Levy I, Rubin LG, Vasishtha S, Tucci V, Sood SK: Emergence of *Candida parapsilosis* as the predominant species causing candidemia in children. Clin Infect Dis 1998; 26: 1086–1088.