Update on invasive fungal infections: the last two years

Carlos Lumbreras[a], Francisco Álvarez-Lerma[b], Enric Carreras[c], José Miguel Cisneros[d], José Garnacho[e], Estrella Martín-Mazuelos[f], Javier Peman[g], Guillermo Quindos[h], Carmen Rubio[i], Julian Torre-Cisneros[j] and Juan Luis Rodríguez Tudela[k]

[a]Unidad de Enfermedades Infecciosas. Hospital 12 de Octubre. Madrid. Spain. [b]Servicio de Medicina Intensiva. Hospital del Mar. Barcelona. Spain. [c]Servicio de Hematología. Hospital Clínic. Barcelona. Spain. [d]Servicio de Enfermedades Infecciosas. Hospital Universitario Virgen del Rocio. Sevilla. Spain. [e]Servicio de Cuidados Intensivos. Hospital Universitario Virgen del Rocío. Sevilla. Spain. [f]Servicio de Microbiología. Hospital Universitario Valme. Sevilla. Spain. [g]Servicio de Microbiología. Hospital Universitario La Fe. Valencia. Spain. [h]Departamento de Microbiología & Inmunología. Facultad de Medicina. Universidad del País Vasco. Bilbao. Bizcaia. Spain. [i]Servicio de Microbiología. Hospital Clínico Universitario Lozano Blesa. Zaragoza. Spain. [j]Servicio de Enfermedades Infecciosas. Hospital Reina Sofía. Córdoba. Spain. [k]Servicio de Micología. Centro Nacional de Microbiología. Instituto de Salud Carlos III. Majadahonda. Spain.

Several important changes are taking place in the field of invasive fungal infections. The increasing incidence of invasive fungal infections as a result of progress in areas of medicine such as organ transplantation, cancer therapy or intensive-care medical technology has provided the impetus for a search for a new and more favorable scenario. In addition, pharmaceutical companies have developed new, well-tolerated and more effective broad-spectrum antifungal agents. Therefore, during the last few years, several articles on invasive fungal infections have been published. This review focuses on the new insights in the literature on fungal infections during 2004 and 2005. Three areas of interest have been identified: (i) epidemiology and risk factors, (ii) new diagnostic procedures, and (iii) prevention and treatment. A review of the English-language and Spanish-language literature on invasive fungal infections has been made, and those articles considered essential reading have been reviewed and discussed in order to highlight their original aspects.

Key words: **Invasive fungal infections. Systemic mycoses. Organ transplantation**

Actualización de las infecciones fúngicas invasoras: los dos últimos años

En el campo de las infecciones fúngicas invasoras se están produciendo varios cambios importantes. El aumento en la incidencia de las infecciones fúngicas invasoras a consecuencia de los progresos que se han realizado en áreas de la medicina, como el trasplante de órganos, el tratamiento del cáncer y la tecnología de los cuidados médicos intensivos, ha estimulado la búsqueda de nuevos contextos más favorables. Además, las compañías farmacéuticas han desarrollado agentes antifúngicos de amplio espectro bien tolerados y más eficaces. Así, durante los últimos años se han publicado varios artículos relativos a las infecciones fúngicas invasoras. Esta revisión está fundamentada en las publicaciones relativas a las infecciones fúngicas que han aparecido en la bibliografía médica durante los años 2004 y 2005. Se han identificado tres áreas de interés: *1)* epidemiología y factores de riesgo; *2)* nuevos procedimientos diagnósticos, y *3)* prevención y tratamiento. Se ha realizado una revisión de la bibliografía médica en los idiomas inglés y español relativa a las infecciones fúngicas invasoras, con exposición y discusión de los artículos considerados de lectura obligada en el intento de poner de manifiesto sus aspectos originales.

Palabras clave: **Infecciones fúngicas invasoras. Micosis sistémicas. Trasplante de órganos.**

Introduction

Several important changes are taking place in the field of invasive fungal infections (IFI). The increasing incidence of IFI as a result of the progress in some areas of medicine such as organ transplantation, cancer therapy or intensive-care medical technology, has provided the impetus for a search for a new and more favourable scenario. As a logical result of the renewed interest in the treatment of IFI, pharmaceutical companies have developed new, well-tolerated and more effective broad-spectrum antifungal agents. Moreover, the availability of better antifungal drugs has also stimulated the search for new tools in the early diagnosis of IFI and new therapeutic strategies. Overall, there is increasing evidence that IFI should no longer be considered the final event of patients with severe underlying diseases, but a severe complication which may be prevented or cured.

Correspondence: Dr. J.L. Rodríguez Tudela.
Servicio de Micología. Centro Nacional de Microbiología.
Instituto de Salud Carlos III.
Ctra. Majadahonda Pozuelo, km 2. 28220 Majadahonda. Spain.
E-mail: juanl.rodriguez-tudela@isciii.es

Below, we review what, in our opinion, are the most interesting articles in the IFI field during 2004 and 2005.

Epidemiology and risk factors

During the last two years, several articles on the epidemiology of IFI have been published in the literature. Population-based surveillance studies are able to identify all cases of IFI regardless of the setting. They decrease the bias resulting from the selection of only a subset of hospitals and permit newly affected patient groups to be identified. Therefore, population-based surveillance studies should be the standard for establishing the epidemiology of any infection and for studying the risk factors of the infected population. However, they are expensive and cumbersome, and, therefore, uncommon. As for *Candida* bloodstream infections (BSI), before 2004, several studies were reported in the United States[1,2], but in Europe the studies were limited to Iceland[3] and Finland[4]. In 2005, Almirante et al[5] reported the results of a population-based, active, prospective surveillance study for bloodstream infections caused by *Candida* in Spain, to determine the distribution of the species involved and the prevalence of resistance to antifungals, and to evaluate risk factors for mortality. Furthermore, in Denmark, a semi-national study of candidemia has also been reported[6], as well as other non-population-based prospective multi-center studies[7]. The Spanish study[5] was performed in the Barcelona area with a population of 3.9 million between 1 January 2002 and 31 December 2003. Fourteen hospitals participated (from 214 to 1,295 beds). All blood cultures from which a *Candida* species was isolated were reported and during the first week after the BSI was diagnosed, the infection was confirmed or ruled out. Three weeks later the case report form was completed and the outcome was recorded. Periodic audits of clinical laboratories were performed. To measure severity of illness, the Acute Physiology and Chronic Health Evaluation (APACHE) II score was used for adult patients admitted to ICUs. For adults outside an ICU, the Karnofsky performance status scale was used. However, for pediatric patients, a standardized score of severity of illness was not used. The isolation of any *Candida* species from the blood was defined as a case. A new case was defined as isolation of a *Candida* species > 30 days after the initial case. Cases occurring either prior to or within 2 days of admission were considered community-acquired. A case was defined as likely to be catheter-related when (i) semiquantitative culture of the catheter tip yielded more than 15 CFU of a *Candida* species, or (ii) simultaneous quantitative cultures of blood samples showed a ratio of ≥ 5:1 CFU of blood samples obtained through the catheter and a peripheral vein.

Mortality was classified as follows: (i) early mortality, defined as death occurring 3 to 7 days after diagnosis and, (ii) late mortality, defined as death occurring between days 8 to 30. Mortality during days 1 and 2 were excluded from the analysis. For the late mortality study, adequate treatment was defined as ≥ 5 days of any antifungal medication in addition to catheter removal.

Candida isolates were identified by standard procedures and antifungal susceptibility testing was performed following EUCAST methodology[8,9]. Isolates were classified as showing decreased susceptibility to fluconazole when the MIC was ≥ 16 mg/L.

Statistical analysis was performed using SAS, version 8.2 (SAS Institute, Cary, N.C.). The Chi-square or Fisher exact test was used to compare categorical variables. Univariate and multivariate analyses were performed using the LOGISTIC procedure.

We detected 341 patients with *Candida* BSI. Four patients had a recurrent episode, resulting in a total of 345 cases. The average annual incidence of candidemia was 4.3 cases per 100,000 inhabitants. The incidence rate was highest in infants (38.8 cases per 100,000 inhabitants), and in those aged > 65 years (12 cases per 100,000 inhabitants). Community acquisition accounted for 11% of cases and only 33% of cases of candidemia were diagnosed in an ICU.

Regarding species distribution, the most common isolate was *C. albicans* (51%), followed by *C. parapsilosis* (23%), *C. tropicalis* (10%), *C. glabrata* (9%), and *Candida krusei* (4%). Other *Candida* species were isolated in 11 cases (3%).

In a multivariate analysis excluding *C. parapsilosis* (due to significant differences in demographics and crude mortality), previous treatment with fluconazole (odds ratio [OR] 3.3; 95% confidence interval [CI] 1.8-6.1; $p < 0.01$) was the only exposure significantly associated with non-*C. albicans* candidemia. In addition, previous antibiotic use was a protective factor for non-*C. albicans* candidemia compared with *C. albicans* candidemia (OR 0.4; 95% CI 0.2-0.8; $p < 0.01$).

Mortality within the first 30 days was 44%, and 22% died within 7 days of culture. Multivariate analysis indicated that treatment with an antifungal and having the catheter removed as a part of treatment were independently associated with a lower odds ratio of early death (treatment with an antifungal: OR 0.05; 95% CI, 0.01-0.2; $p < 0.01$; catheter removal: OR 0.3; 95% CI, 0.1-0.9; $p = 0.04$). The same results were obtained for late mortality. Thus, in the multivariate analysis, only intubation (OR 7.5; 95% CI, 2.6-21.1; $p < 0.01$) and adequate treatment (OR 0.2; 95% CI, 0.08-0.8; $p < 0.01$) were independent predictors of late mortality. Multivariable analysis indicated that treatment with an antifungal and having the catheter removed as a part of treatment were independently associated with a lower odds of early death (treatment with antifungal: OR 0.05; 95% CI, 0.01-0.2; $p < 0.01$; catheter removal: OR 0.3; 95%CI, 0.1-0.9; $p = 0.04$.). On the contrary having a haematological malignancy was associated with greater odds (OR 3.5; 95% CI, 1.1-10.4; $p = 0.03$). Same results were obtained for late mortality. Thus, in multivariate analysis, only intubation (OR 7.5; 95% CI, 2.6-21.1; $p < 0.01$) and adequate treatment (OR 0.2; 95% CI, 0.08-0.8; $p < 0.01$) were independent predictors of late mortality.

Antifungal susceptibility testing is well recorded in a study by Cuenca-Estrella et al[10], in which amphotericin B and flucytosine were active in vitro against all strains. A total of 24 strains (6.8%) showed decreased susceptibility to fluconazole (MIC ≥ 16 mg/L) and 43 (12.3%) showed decreased susceptibility to itraconazole (MIC ≥ 0.25 mg/L). Voriconazole and caspofungin were active in vitro against most isolates, even those that were resistant to fluconazole.