Invasive candidiasis in the neutropenic patient

ABSTRACT

There are major differences in the epidemiology and prognosis of invasive candidiasis and candidemia in the neutropenic patient; however, a recent study performed in Spanish hospitals (Candipop) confirmed that mortality at 1 month is 30%, which is similar to that observed in the general population. Although Candida albicans is the most frequently isolated species, C. tropicalis, C. glabrata, and C. krusei are more prevalent than in non-neutropenic patients. The benefit of neutrophil transfusion is unclear, and catheter withdrawal must be tailored and based on confirmation of the diagnosis. Echinocandins are the first-line option for therapy and have a better safety profile than other agents.

EPIDEMIOLOGY

The Candipop study, which recently analysed 752 episodes of candidemia in 29 Spanish hospitals between April 2010 and March 2011, confirmed that mortality was 30% during the first 30 days and 13% during the first week after diagnosis. The independent factors associated with mortality during the first 7 days were age, primary origin of candidemia, presence of septic shock, and administration of the appropriate antifungal drug. Withdrawal of the catheter did not reduce mortality overall, although early withdrawal did (first 48 hours). In patients with oncologic-hematologic conditions, the factors associated with mortality were similar to those of the general population. However, compared with patients with solid tumours, patients with hematologic neoplasms had a significantly higher incidence of candidemia and a lower frequency of catheter-associated candidemia and required the catheter to be withdrawn less often. This less relevant role of the catheter as the origin of candidemia in patients with haematological disease has also been confirmed elsewhere.

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RESUMEN

Existen diferencias significativas en la epidemiología y pronóstico de la candidemia y candidiasis invasiva en el paciente neutropénico, aunque una similar mortalidad a la observada en la población general (30% al mes) ha sido notificada en un reciente estudio nacional (Candipop). Candida albicans es la especie más frecuente pero C. tropicalis, C. glabrata y C. krusei tienen una mayor prevalencia que en los pacientes no neutropénicos. No está claro el beneficio de la transfusión de neutrófilos y la retirada de catéter debe ser individualizada. Las equinocandinas suponen el tratamiento de elección dada su eficacia y perfil de toxicidad en relación a otros antifúngicos.
RECOMMENDATIONS ON TREATMENT OF INVASIVE CANDIDIASIS AND CANDIDEMIA IN PATIENTS WITH ONCOLOGIC-HAEMATOLOGIC DISORDERS

Several clinical guidelines and national and international consensus statements have been published in recent years7-12.

In 2012, ESCMID published specific guidelines on the management of candidemia in patients with hematologic cancer who had undergone bone marrow transplantation9. The guidelines do not recommend prophylaxis for post-chemotherapy neutropenia or in autologous transplantation. However, they do justify prophylaxis in allogeneic transplantation in the following situations: neutropenia (recommendation grade AII for fluconazole, posaconazole, voriconazole, and micafungin), during the first 100 days in the absence of graft-versus-host disease (GVHD) (recommendation grade AI for fluconazole and posaconazole) and in the presence of GVHD (recommendation AI for fluconazole and posaconazole). In the case of empiric treatment for patients with long-term neutropenia, their highest recommendation is caspofungin (AI) and micafungin (AI), followed by liposomal amphotericin B (BI), fluconazole (CII), posaconazole (CII), and voriconazole (DI). For targeted treatment, the guidelines suggest caspofungin (AI) or liposomal amphotericin B (AI) and recommend catheter withdrawal (AI). Lastly, transfusion of granulocytes is considered a last resort in some cases of candidemia/candidiasis in neutropenic patients (CIII).

In 2016, the Infectious Diseases Society of America (IDSA) re-edited its guidelines on candidemia in the general population and for different conditions, including neutropenia12. Table 1 summarizes the main recommendations. Of particular interest is the recommendation of echinocandins as initial therapy and stepping down to fluconazole after recovery from neutropenia in clinically stable patients infected by a sensitive strain. The recommendations give more weight to transfusion of granulocytes, although the recommendation is weak and the level of evidence low; however, withdrawal of the catheter is recommended on an individual basis (strong recommendation, low level evidence).

ROLE OF WITHDRAWAL OF INTRAVENOUS CATHETER IN PATIENTS WITH ONCOLOGIC-HAEMATOLOGIC DISEASES AND CANDIDEMIA

Various studies have confirmed that systematic early withdrawal of vascular catheters in patients with candidemia reduces mortality13-16 and this recommendation is included in most guidelines7-12.

However, systematic withdrawal of vascular catheters has been criticized in patients with candidemia. Nucci et al analysed the impact of catheter withdrawal in two multicentre studies17: a 2-armed study comparing micafungin and liposomal amphotericin B18 and a 3-arm study comparing 2 doses of micafungin (100 mg/d and 150 mg/d) with caspofungin 50 mg/d19. The catheter was removed during the first 48 hours in 354 of 842 evaluable patients and after 48 hours in 180 patients; it was left in place in 308 patients. The univariate analysis showed this approach to be successful and survival at 28 and 42 days to be higher in cases where the catheter was left in place. However, catheter removal did not affect control of recurrent candidemia or microbiological eradication. Finally, the multivariate analysis did not confirm an independent association between catheter withdrawal and success of therapy or survival at 28 or 42 days. Only neutropenia, a high APACHE score, and advanced age were significant.

The apparent discrepancy between the results of this study and other similar studies lies in the differences in prevalence of the intravenous catheter as the source of candidemia. Studies in which the intravascular catheter is the main source of candidemia in >40% of cases (eg, on medical wards or in intensive care units) show that controlling the site of infection by withdrawing the catheter provides clear benefits. However, in situations where the

Table 1  Recommendations on treatment of candidemia in neutropenic patients (adapted from reference 12; IDSA 2016 guidelines, GRADE protocol)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence</th>
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</thead>
<tbody>
<tr>
<td>1 Echinocandins: initial treatment</td>
<td>Strong</td>
</tr>
<tr>
<td>2 Lipid amphotericin B: alternative (greater toxicity)</td>
<td>Strong</td>
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<tr>
<td>3 Fluconazole: alternative (no previous azole therapy, noncritical patient)</td>
<td>Weak</td>
</tr>
<tr>
<td>4 Fluconazole/voriconazole: step down (if sensitive strain, no neutropenia, control of candidemia, noncritical patient)</td>
<td>Weak</td>
</tr>
<tr>
<td>5 Voriconazole: alternative (if also necessary to cover filamentous fungi)</td>
<td>Weak</td>
</tr>
<tr>
<td>6 If Candida krusei: echinocandins, lipid amphotericin B, or voriconazole</td>
<td>Strong</td>
</tr>
<tr>
<td>7 Duration of treatment: 2 weeks (if candidemia is controlled, no distant foci, clinical improvement)</td>
<td>Strong</td>
</tr>
<tr>
<td>8 Ophthalmological examination after resolution of neutropenia</td>
<td>Strong</td>
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<tr>
<td>9 Withdrawal of venous catheter on an individual basis</td>
<td>Strong</td>
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<tr>
<td>10 Granulocyte transfusion: if persistent candidemia and neutropenia</td>
<td>Weak</td>
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</table>
origin of candidemia may be endogenous and not vascular, such as in the neutropenic patient or in patients admitted to surgical wards, prevalence is lower, and recommendations on catheter withdrawal should be tailored after application of diagnostic techniques, including differential blood cultures.

**NEUTROPHIL TRANSFUSION**

Three single-centre retrospective studies have highlighted the key role of neutrophil transfusion in control of candidemia in the neutropenic patient. A similar protocol was applied in all three studies, namely, donors received granulocyte colony-stimulating factor (600 µg), dexamethasone (8 mg), and a high number of transfusions (>8 per patient) with a high neutrophil count (>50 x 10⁹). All 3 studies reported control of candidemia in >50% of cases and a frequency of adverse effects <10% with respect to the low baseline percentage of cross-matching and anti-polymorphonuclear antibodies.

The only multicentre randomized trial to evaluate the role of granulocyte transfusion in neutropenic patients with candidemia was performed with 74 adult patients in Germany. Dexamethasone was not used, and the richness of the polymorphonuclear cells in the units transfused and the frequency of transfusion were lower than in previous studies. The study did not establish significant differences in control of candidemia, and survival at 28 days was similar to that of the control group (82% vs. 84%). In addition to these limitations, the authors also report major limitations (eg, low-risk population, delay between randomization and transfusion), which made it difficult to reach robust conclusions, and agree that new studies are necessary.

**KEY ROLE OF ECHINOCANDINS IN THE TREATMENT OF CANDIDEMIA IN THE NEUTROPENIC PATIENT**

A recent meta-analysis of 1,915 patients with candidemia confirmed that treatment with echinocandins was an independent factor associated with low mortality (OR, 0.65; 95%CI, 0.45-0.94), as was catheter withdrawal (OR, 0.50; 95%CI, 0.35-0.72). Most clinical trials on administration of fluconazole to treat candidemia carried out some years ago excluded neutropenic patients, and no controlled clinical trials with liposomal amphotericin were performed before the advent of the echinocandins.

In the study by Mora et al (caspofungin vs conventional amphotericin to treat candidemia), 13% and 9% of patients, respectively, were neutropenic, and the response in this subgroup was 50% and 40%, which was slightly lower than that observed in the overall population (73% and 62%, respectively).

Kuse et al (micafungin vs liposomal amphotericin in candidemia) also included a significant number of neutropenic patients (12% and 8%, respectively) and confirmed a response of 75% and 80%, which was similar to that obtained in the overall population.

Papas et al (micafungin 100 mg/d vs micafungin 150 mg/d vs caspofungin 50 mg/d in patients with candidemia) found that 11%, 9%, and 6% of patients were neutropenic, with a response of 82%, 53%, and 64%, respectively.

Reboli et al (anidulafungin vs fluconazole for treatment of candidemia) found that the number of neutropenic patients in both arms was ≤3%, thus precluding evaluation of the role of anidulafungin in this type of patient.

Finally, Walsh et al found a 67% response to caspofungin (vs 50% for liposomal amphotericin B) in neutropenic patients with confirmed candidemia and fever receiving empirical treatment.

A recent meta-analysis including various of the studies mentioned above specifically analysed the key role of echinocandins in patients with neutropenia and revealed a nonsignificant difference in favour of treatment with echinocandins (OR, 0.73; 95%CI, 0.42-1.29), with a clearly beneficial safety profile.

**REFERENCES**


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