CRITICAL CARE

COMMENTARY

Treatment of candidemia in adult patients without neutropenia - an inconvenient truth

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Abstract

In 2009 the Infectious Diseases Society of America reviewed the guidelines on the treatment of candidemia in non-neutropenic patients. In this document the preferred treatment was either fluconazole or an echinocandin. Amphotericin-B formulations were considered an alternative. However, careful assessment of published data showed similar efficacy between these drugs.

Introduction

Fungal infections, in particular candidemia, are a growing problem in immunocompetent patients [1]. Despite several guidelines, concern exists on the value of evidence supporting recommendations for the optimal treatment of candidemia in non-neutropenic adult patients [1,2].

In the midst of this controversy a critical reappraisal of the 2009 Infectious Diseases Society of America (IDSA) guidelines is appropriate [1]. Although many relevant aspects of the guidelines are thoroughly discussed, there are three topics that deserve a closer look: the weight and quality of the evidence; the evidence of efficacy; and the evidence of amphotericin-B (AmB)-induced renal failure.

What is recommended by the 2009 IDSA guidelines?

In 2009, IDSA updated their 2004 guidelines (Table 1) [1,2]. The primary recommendation for treatment of candidemia in non-neutropenic patients was administration of fluconazole or an echinocandin. The alternative approach was administration of lipid formulation (LF)-AmB, AmB-deoxycholate (AmB-d) or voriconazole. The recommendation for echinocandins was extended to patients with moderately severe to severe illness or with recent azole exposure.

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A critical review of the evidence

The 2009 IDSA guidelines [1] represent a marked change in the recommended therapeutic approach, and is not supported by the efficacy of the different antifungals. In all nine clinical trials, AmB-d and LF-AmB were never inferior to any comparator and two recent meta-analyses showed the same results [3,4]. The use of AmB-d and LF-AmB are supported by very solid data from well designed clinical trials and that have consequently been twice graded A-I [1]. Moreover, echinocandins are not suitable for the treatment of endophtalmitis, meningitis and endocarditis [5] whilst AmB remains the drug of choice.

Therefore, even though not explicit in the guidelines, the change is probably related to a possible advantage of echinochandins and the perceived renal dysfunction associated with AmB. In fact, the 2009 IDSA guidelines [1] attribute to AmB-d therapy a high risk of acute renal failure (ARF) and mortality.

The new evidence

A recent study from Reboli and colleagues [6] suggests that anidulafungin might be superior to fluconazole as primary therapy for candidemia in non-neutropenic patients (75.6% success with anidulafungin compared to 60.2% with fluconazole). However, in a noninferiority trial, only noninferiority can be demonstrated and any benefit of the new treatment should be interpreted with great caution [7] and only be based on other advantages, such as safety, convenience and cost [8]. Besides, the evaluation of the primary end-point was made at the end of intravenous therapy, after a median of 14 days of anidulafungin against only 11 days of fluconazole. In addition, more patients in the anidulafungin group had their central venous catheter removed than in the fluconazole arm (96% versus 89%). Consequently, as Sobel and Revankar wrote in an editorial [9], anidulafungin was, at best, noninferior in comparison to fluconazole.

The myths on nephrotoxicity

The change of the positioning of AmB preparations in the 2009 guidelines [1,2] seems to be supported by the nephrotoxicity findings of two studies, one showing that

Table 1. Infectious Disease Society of America guidelines for the treatment of candidemia in non-neutropenic adult patients [1,2]

	2004	2009
Recommended therapy	AmB-d 0.6 to 1 mg/kg/day Fluconazole 400 to 800 mg/day Caspofungin 50 mg/day (70 mg first dose)	Echinochandin[a]: Caspofungin 50 mg/day (70 mg first dose) Anidulafungin 100 mg/day (200 mg first dose) Micafungin 100 mg/day Fluconazol 6 mg/kg/day (12 mg/kg first dose)
Alternative therapy	AmB-d 0.7 mg/kg/day + Fluconazol 800 mg/day (4 to 7 days, then Fluconazol 800 mg/day)	LF-AmB 3 to 5 mg/kg/day AmB-d 0.5 to 1 mg/kg Voriconazol 3 mg/kg bid (6 mg/kg first two doses)
Duration of therapy	At least 14 days after last positive blood culture	At least 14 days after last positive blood culture
Other recommendations	Removal of central venous catheter Ophthalmological evaluation	Removal of central venous catheter Ophthalmological evaluation

[a]An echinochandin was also recommended in moderate to severe infection or with recent azole exposure. AmB-d, Amphotericin-B deoxycholate; LF-AmB, lipid formulation Amphotericin-B.

Table 2. Amphotericin-B nephrotoxicity; data cited in 2009 Infectious Disease Society of America guidelines [1]

	Wingard *et al.* [12]	Bates *et al.* [11]
Year of publication	1999	2001
Data collection	Jan 1991 to Dec 1993	May 1993 to Apr 1997
Inclusion criteria	1. Allogeneic BMT 2. Autologous BMT 3. Solid organ transplantation 4. Immunosuppressive conditions not related to transplantation	Not patients but number of admissions; at least 156 repeated measurements; major violation of the assumptions of statistical methods used
Infection	Aspergillosis	Unknown
Duration of AmB (days)	20.4	14.8
AmB cumulative dose (g)	Unknown	0.93
AmB daily dose (mg/kg)	Unknown	Unknown
Concomitant nephrotoxic agents	87%	Collected (not given)
Risk of death	HD >3×	ARF >6.6×

AmB, Amphotericin-B; ARF, acute renal failure defined as a 50% increase in the baseline creatinine level, with a peak of >2.0 mg/dL; BMT, bone marrow transplant; HD, haemodialysis.

AmB-d could result in ARF in up to 50% of patients [10] and the other that AmB-d-induced nephrotoxicity is associated with a 6.6-fold increased risk of death [11] (Table 2).

The first study is a review about AmB nephrotoxicity [10]; in this review, the author cited another study published in 1999 [12] where those findings were presented. However, patients included in this retrospective analysis were markedly immunosupressed, received concomitantly nephrotoxic agents, and received long courses of AmB (20.4 days) for suspected or proven aspergillosis, not invasive candidiasis. Accordingly, these findings cannot be extrapolated to non-neutropenic patients with candidemia.

The second study [11] is also a retrospective analysis published in 2001, using data from 707 admissions of 551 patients treated with AmB-d. However, the inclusion of the same patient several times constitutes a major violation of the assumptions necessary to compare groups with the statistical methods used. Roughly, 30% of these admissions were complicated with ARF. The average highest creatinine in this group was 3.3 ± 1.3 mg/dL, whereas in those without ARF it was 1.6 ± 0.7 mg/dL ($P < 0.0001$). The mortality rate in the admissions complicated with ARF was 54.2% and in those without ARF it was only 16% (odds ratio for death, 6.6). From these data, it is difficult to envisage that patients with a mean increase in creatinine of 1.7 mg/dL had a 6.6-fold increased risk of death.

Besides, as we have already pointed out, AmB was never inferior to any comparator in six randomised controlled trials with non-neutropenic adult patients with candidemia [3,4]. If AmB-induced nephrotoxicity was so common and has such a detrimental effect on prognosis, it would be expected that this finding would have a negative effect on mortality.

Should we still use AmB-d?

Even though AmB-d is an old drug, it is still regarded as one of the drugs of choice for treatment of

life-threatening mycoses as well as for the empirical therapy of febrile neutropenia. A Cochrane review published in 2000, but left unchanged after reassessments in 2007 and in 2009, provides support for this practice [13]. That is probably because AmB-d remains the antifungal with the most rapid time-kill rate and the largest post-antifungal effect [14] and with efficacy that increases with its concentration [15]. LF-AmB could present a better safety profile, but its cost constitutes a major limitation to its routine use. In addition, there are no solid data to support any benefit from LF-AmB in comparison to AmB-d if administered with correct pre-medication.

Conclusion

Careful assessment of published data on the treatment of candidemia in non-neutropenic patients showed similar efficacy between AmB preparations, fluconazole and echinochandins. The choice of first line therapy should be based on individual risk factors, patterns of *Candida* susceptibility, clinical experience, as well as local availability of the different drugs and their costs.

Abbreviations

AmB, amphotericin-B; AmB-d, amphotericin-B deoxycholate; ARF, acute renal failure; IDSA, Infectious Diseases Society of America; LF-AmB, lipid formulation of amphotericin-B.

Competing interests

PP has received honoraria and served as advisor of Astra Zeneca, Ely-Lilly, Gilead, Janssen-Cilag, Merck Sharp and Dohme, Novartis and Pfizer. JGP has received honoraria and served as advisor of Pfizer, Astra-Zeneca, Abbott, Wyeth-Lederle, Janssen-Cilag, Merck Sharp and Dohme, and received an unrestricted research grant from Astra-Zeneca.

Authors' contributions

PP and JGP contributed to the conception, analysis and interpretation of data of the present commentary and were involved in drafting the manuscript and its revision.

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