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Review article

Does the current treatment of invasive fungal infection need to be reviewed?

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ABSTRACT

Invasive fungal infections (IFIs) are becoming more frequent due to the increasing number of patients at risk. Over the last decade, their prognosis has improved with the diagnostic and therapeutic advances, including new antifungals. In the two years, from 2007 to 2009, antifungal consumption increased by 27%, 67 times more than antibacterial consumption, albeit with great differences between hospitals. The scientific evidence of the indications for antifungal prophylaxis and targeted antifungal therapy is strong; however, it is weak for empirical antifungal therapy, which is the most common indication. Antifungals are not harmless, since they are associated with a wide range of adverse effects and drug interactions, favor the development of resistance, contribute to other fungal superinfections and cause significant healthcare spending.

Therefore, the question arises whether this extraordinary increase in consumption is justified, whether the use of antifungals is optimal, or whether it is necessary to reconsider the current treatment of IFIs instead.

¿Es necesario reconsiderar el tratamiento actual de la infección fúngica invasora?

Palabras clave:
Terapia antifúngica
Consumo de antifúngicos
Infección fúngica invasora

RESUMEN

Las infecciones fúngicas invasoras (IFIs) son cada vez más frecuentes debido a un aumento pacientes en riesgo. En la última década, su pronóstico ha mejorado con los avances diagnósticos y terapéuticos, incluyendo los nuevos antifúngicos. En dos años, de 2007 a 2009, el consumo antifúngico aumentó un 27%, 67 veces más que el consumo de antibacterianos, aunque con grandes diferencias entre hospitales. La evidencia científica de las indicaciones de profilaxis antifúngica y terapia antifúngica dirigida es fuerte, sin embargo es débil para la terapia antifúngica empírica, que es la indicación más común. Los antifúngicos no son inofensivos ya que se asocian efectos adversos e interacciones medicamentosas, favorecen el desarrollo de resistencias, contribuyen a otras sobreinfecciones micóticas y causan un importante gasto sanitario.

Por lo tanto, la pregunta que surge es si este aumento extraordinario del consumo se justifica, si el uso de antifúngicos es óptimo o si es necesario reconsiderar el tratamiento actual de las infecciones fúngicas invasoras.

Introduction

Over the last two decades, the incidence of invasive fungal infection (IFI) has increased due to the advances in medicine resulting in increased life expectancy of immunocompromised and critically ill patients at high risk for IFI.[1–3] In hematological patients, invasive aspergillosis (IA) is currently the most frequent IFI. Its incidence is much higher in patients with acute myeloblastic leukemia (AML) and allogeneic hematopoietic stem cell transplantation (HSCT) recipients, reaching 10.9%, and with an attributable mortality as high as 77% in allogeneic HSCT recipients.[1,4–9] In other immunocompromised patients as solid-organ transplant (SOT) (other than lung) recipients, invasive candidiasis (IC) is the most frequent fungal infection.[2] In critically ill patients IC, mostly presented as candidemia, is the most common IFI with a reported prevalence of 6.9–10.08 episodes/1000 intensive care units (ICUs) admissions

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Table 1
Incidence of invasive fungal infection (IFI) and IFI attributable mortality in different groups of patients.

Patient	IFI incidence (%)			IFI attributable mortality (%)			Ref.
	IA[a]	IC[b]	Other moulds	IA	IC	Other moulds	
Hematological patients	2.6	1.5	0.2[f]	42	33	58.6[f]	4
AML[c]	7.1	4.1–6.9	0.7[f]	38	34.4–35.5	59.1[f]	4,9
HSCT recipients[d]	2.6	0.9	0.15[g]	72.1	50	40[g]	5
Allogeneic HSCT	6.3	1.1–1.9	0.4[g]	77.2	53.8–57.1	40[g]	5,9
SOT recipients[e]	0.8	2.4	0.4	41[j]	34[j]	39[j]	2
Critical patients	6.3[h]	10.1[h]	–	63[i]	46[i]	–	11

[a] IA: invasive aspergillosis.
[b] IC: invasive candidiasis.
[c] AML: acute myeloblastic leukemia.
[d] HSCT recipients: hematopoietic stem cell transplant recipients.
[e] SOT recipients: solid organ transplant recipients.
[f] Other moulds composed by *Fusarium* species and *Zygomycetes* species.
[g] Other moulds composed by *Fusarium* species, *Scedosporium* species and *Mucor* species.
[h] Average rate of invasive fungal infection episodes/1000 admissions.
[i] Crude mortality rate at 30 days.
[j] Crude mortality 12 months after infection.

and crude mortality rate ranging from 42 to 46%.[10,11] The IFI incidence and IFI attributable mortality in the most important risk groups of patients are specified in Table 1.

Facing the need to combat IFI, from 1990s a growing arsenal of new antifungal drugs have been authorized by the European Medicine Agency for prophylaxis, empirical or targeted antifungal therapy contributing to reduce the IFI attributable mortality.[8,12] However, antifungal therapy is not exempt from risks as hepatotoxicity or nephrotoxicity, and infusion related reactions are common (up to 45.5%) and may be severe. Discontinuation due to adverse effects reaches up to 18.6% in clinical trials[13–15]; side effects such as nephrotoxicity of amphotericin and pharmacologic interactions between azoles and immunosuppressants agents are a frequent problem especially in HSCT and SOT recipients[13,14,16]; and previous azole exposition may lead to emergence of *Candida* spp. resistance[17] or breakthrough mucormicosis.[18] Moreover, the growth of antifungal consumption in health care has become an important health spending[19,20] turning the optimization of antifungal therapy into a priority for health care systems.

Facing this scenario the question then arises: 'Are we using antifungal drugs appropriately?'

Antifungal consumption and suitability of the indication

Antifungal consumption has risen continuously in recent years, particularly since the approval of the echinocandins. In a study conducted in five German hospitals between 2001 and 2003, the antifungal consumption increased by 13.4% with great differences among centers.[19] This increase in the consumption of antifungal drugs is 67 times higher than the increase of the consumption of antibacterial drugs. In a multicenter study conducted by the Spanish Network for Research in Infectious Diseases (REIPI) during the years 2007–2009, an increase of the antifungal consumption of 27% of defined daily dose/100 occupied bed-days (DDD/100 OBD) was observed, compared to an increase in the antibacterial consumption of 0.4% DDD/100 OBD. Also, the variability of the antifungal consumption among the participating centers was 9-fold higher than variability in antibacterial consumption.[21] Other studies in American hospitals confirmed the great increase in the consumption of antifungals and the large variability intercenters.[19,22] The burden of antifungal consumption is different for each indication of antifungal prophylaxis and empirical and targeted antifungal therapy. Although there are only limited published data about the distribution of antifungal consumption,[23,24] we may infer it from the above mentioned study.[21] According to a standard hospital of 1200 beds with 84% occupancy, antifungal consumption represents 5.6 DDD/100 OBD. Considering a reported incidence of 0.14 episode/day of therapy for candidemia and 0.12 episode/day of therapy for IA,[25,26] the expected targeted antifungal therapy should be 0.26 DDD/100 OBD for each IFI. The remaining antifungal consumption, approximately 5.0 DDD/100 OBD, must be spent for both antifungal prophylaxis and especially in empirical antifungal therapy (EAT). Although it should be noted that most of the antifungal consumption in the prophylaxis indication is carried out in outpatients, and therefore it is not included in the evaluation of consumption in DDD/100 OBD.

The use of antifungals remains still a room for improvement. The results of a study performed in the ICU and oncohematology department of a French hospital showed that 40% of the antifungal therapies indicated were inappropriate.[23] Moreover, 48% of the antifungal indications in a multicenter study carried out in 147 Spanish ICUs were empirical.[27]

Furthermore, the cost of antifungals significantly impact on the overall antimicrobial budget. Data from the implementation of an antimicrobial stewardship program in a large tertiary hospital, during seven years, indicated that the average rate of the antifungal cost represented 29.5% of the overall antimicrobial expenditure ranging from 47.7% ($3.7 million) to 18.8% ($1.2 million) before and after the program implementation.[28]

Despite the vast inpatient antifungal consumption used for empirical therapy, this indication lacks of a high level of scientific evidence[29–33] (Table 2). We will review below said indications of EAT, in the neutropenic patient and the critically ill patient, and the targeted antifungal therapy.

Empirical antifungal therapy in neutropenic patients

The main risk factor for IFI in neutropenic hematological patients is profound and prolonged neutropenia, and the most common clinical presentation is neutropenic fever. Since the main objective of the EAT is to improve IFI prognosis with prompt therapy, universal EAT in neutropenic patients after 5–7 days of persistent fever has been traditionally recommended by the main scientific societies. Scientific evidence supporting this recommendation is weak and based on two clinical trials with small sample size and questionable methodology that compared the administration of amphotericin *vs.* placebo and failed to demonstrate significantly reduced IFI incidence or IFI related mortality.[34,35] Subsequently there have been several large comparative studies to identify which is the best drug for EAT,[13–15,36–39] but no