J Antimicrob Chemother 2016; **71** Suppl 2: ii43–ii44
doi:10.1093/jac/dkw396

Journal of Antimicrobial Chemotherapy

Conclusion and future perspectives on antifungal stewardship

Jose María Aguado[1]*, Jose Tiago Silva[1] and Emilio Bouza[2]

[1]*Unit of Infectious Diseases, Hospital Universitario '12 de Octubre', Instituto de Investigación Hospital '12 de Octubre' (i+12), School of Medicine, Universidad Complutense, Madrid, Spain;* [2]*Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario 'Gregorio Marañón', Instituto de Investigación Sanitaria Gregorio Marañón, Department of Medicine, Universidad Complutense, Madrid, Spain*

*Corresponding author. Tel: +34 91 39 08 00; Fax: +34 91 469 57 75; E-mail: jaguadog1@gmail.com

The term 'invasive fungal disease' (IFD) encompasses a wide range of fungal infections, ranging from candidiasis to aspergillosis, and from cryptococcosis to mucormycosis.[1] The risk factors and patient populations at risk of developing fungal infections also vary between different fungal species. For example, *Aspergillus* is more common in patients with haematological malignancies (allogeneic stem cell transplant recipients or patients receiving chemotherapy for acute myeloid leukaemia) and in lung transplant recipients,[2] while cryptococcosis is historically associated with patients diagnosed with AIDS.[3] Invasive candidiasis (IC) and candidaemia can be considered good examples of the potential pitfalls in the use and misuse of antifungal agents, and also of the limited guidance that is available in how to reduce catheter-related infections.

There are a variety of challenges related to improving treatment for patients with IFD. For example, IFDs frequently present with non-specific clinical manifestations, early diagnosis is often difficult, and there is likely to be a high risk of toxicity and side effects associated with antifungal treatment.[4,5] This Supplement highlights the key factors for consideration for optimal treatment of IFD, focusing on current issues with diagnosis, improvements in treatment and the need to encourage effective and practical multidisciplinary plans for the implementation of antifungal stewardship (AFS) programmes.

With regard to diagnosis, a recent study in 219 high-risk haematological patients demonstrated that a combination of the serum galactomannan (GM) assay and PCR-based detection of *Aspergillus* DNA in blood was associated with an earlier diagnosis of invasive aspergillosis (IA).[6] The *Aspergillus* lateral-flow device could also be an effective diagnostic tool for IA, due to its high specificity, point-of-care diagnostic potential and reduced time to perform when compared with the GM assay.[7] As alluded to in this Supplement by Maertens *et al*.,[8] other biomarkers that may be useful for the diagnosis of IA are also in development, such as the electronic nose (eNose) or the detection of bis(methylthio)gliotoxin (bmGT). It is also important to note that in recent years, several non-culture-based tests for the diagnosis of IC have been developed. 1,3-β-D-Glucan (BDG) testing, PCR-based tests and detection of *Candida* mannan/antimannan antibodies in serum have been evaluated, showing a high negative predictive value for the diagnosis of IC;[9–11] PCR could therefore be an efficacious test for promptly detecting *Candida* infection.[12] *Candida* antibody detection kits are also under evaluation. As mentioned by Lortholary *et al*.,[13] it has been demonstrated that a multiplex quantitative PCR targeting 18S rDNA of *Mucor* spp./*Rhizopus* spp., *Lichtheimia* complex and *Rhizomucor* spp. in combination may be an effective diagnostic test to facilitate the early diagnosis of mucormycosis and serve as a model for the diagnosis of other fungal infections.[14] Semi-quantitative tools for detection of cryptococcal polysaccharide antigen (CRAG) are also currently under evaluation to help improve the diagnosis of latent cryptococcal meningitis. These tools may have the potential to help improve the prognosis of patients, allowing earlier diagnosis and treatment; however, most of these tools are not yet available in the majority of centres.

With regard to treatment, recent improvements in antifungal drugs have significantly improved the prognosis of high-risk patients. As discussed by Bassetti *et al*.[15] in this Supplement, echinocandins have a strong fungicidal and biofilm activity, especially against *Candida*, without the toxicity and side effects associated with azoles and amphotericin B. These are now recommended as first-line drugs for the treatment of IC and candidaemia.[16]

However, despite the advances in the diagnosis and treatment of IFD in recent years, new challenges are currently being faced in the management of IFD. One of the main questions today relates to the costs associated with the management of these diseases. The treatment of IFD is usually expensive and resources are often limited. The importance of attaining a cost-effective treatment for patients has encouraged the development of multidisciplinary teams and AFS programmes. As mentioned by Agrawal *et al*.[17] in this Supplement, multidisciplinary teams with clinical expertise in the management of IFD, as well as extensive knowledge of fungal epidemiology and antifungal treatment options, are of great value when considering how to optimize care for patients.[18–20] These teams should be responsible for implementing local AFS programmes, as referred to by Muñoz and Bouza,[21] through a close and continuous collaboration with different medical specialties (haematology, intensive care, internal medicine, etc.). Multidisciplinary teams are able to advise on the most appropriate antifungal drug depending on the type of patient/infection, e.g. by replacing inappropriate and expensive antifungal drugs with those that may be less costly but equally effective, but also in deciding

which patients would benefit from antifungal prophylactic regimens or when an empirical antifungal treatment could be safely withdrawn. Multidisciplinary teams can also advise on which diagnostic tests are most appropriate for each patient, as well as aiding in their interpretation. Several studies have proved that multidisciplinary teams and AFS programmes are extremely effective in reducing the costs associated with the management of IFD, although this effect often diminishes once their advisory work is discontinued.[22,23] Another potential key advantage of these programmes is that encouraging the appropriate use of antifungal drugs will likely limit, and possibly decrease, the emergence of antifungal resistance, which is currently a major concern in relation to the treatment of IFD. The authors believe that, in the future, all hospitals should have their own antifungal multidisciplinary team and a corresponding AFS programme.

In summary, the diagnosis and treatment of IFD remains challenging, and IFDs are often still associated with significant morbidity and mortality.[1] Although new diagnostic tests, such as BDG or PCR, and the extended use of prophylactic regimens and empirical treatment have reduced the burden of IFD, the treatment of these diseases is still associated with significant challenges and costs. It appears advisable to implement multidisciplinary teams and AFS programmes in order to encourage the appropriate use of resources, with the aim of optimizing patient care in a cost-effective manner.

Transparency declarations

J. M. A. has received honoraria for speaking at symposia organized on behalf of Pfizer, Merck Sharp & Dohme (MSD), Schering-Plough, Roche, Astellas Pharma, and Gilead Sciences; and has sat on advisory boards for antifungal agents on behalf of MSD, Astellas Pharma, Pfizer, Roche, Chimerix, and Gilead Sciences. E. B. has participated in meetings and advisory boards for Pfizer, Novartis, Janssen, Baxter, McDonalds, Astellas, Wyeth Lederle, Optimer, several scientific societies and non-profit foundations (Fundación de Ciencias de la Salud); received research funds from Pfizer, Astra-Zeneca, Novartis, Schering-Plough, Covidien, FIS, CIBER Enf Respiratorias, REIPI, Mutua Madrileña, European Community funds, Fundación del Pino; and received payment for conferences from Pfizer, Novartis, Astellas, Wyeth Lederle and other private and public sources. J. T. S. holds a research contract from the 'Spanish Network for Research in Infectious Diseases' (REIPI).

This article forms part of a Supplement sponsored and funded by Gilead Sciences Europe Ltd; editorial assistance was provided by Synergy Medical. The content of this Supplement is based on the sessions presented at the CARE VIII meeting, held in Madrid in November 2015.

References

1 Kim JY. Human fungal pathogens: why should we learn? *J Microbiol* 2016; **54**: 145–8.

2 Segal BH. Aspergillosis. *N Engl J Med* 2009; **360**: 1870–84.

3 Maziarz EK, Perfect JR. Cryptococcosis. *Infect Dis Clin North Am* 2016; **30**: 179–206.

4 Aye C, Henderson A, Yu H *et al*. Cryptococcosis—the impact of delay to diagnosis. *Clin Microbiol Infect* 2016; **22**: 632–5.

5 Gaona-Flores VA, Campos-Navarro LA, Cervantes-Tovar RM *et al*. The epidemiology of fungemia in an infectious diseases hospital in Mexico city: a 10-year retrospective review. *Med Mycol* 2016; **54**: 600–4.

6 Aguado JM, Vazquez L, Fernandez-Ruiz M *et al*. Serum galactomannan versus a combination of galactomannan and polymerase chain reaction-based *Aspergillus* DNA detection for early therapy of invasive aspergillosis in high-risk hematological patients: a randomized controlled trial. *Clin Infect Dis* 2015; **60**: 405–14.

7 Thornton CR. Development of an immunochromatographic lateral-flow device for rapid serodiagnosis of invasive aspergillosis. *Clin Vaccine Immunol* 2008; **15**: 1095–105.

8 Maertens JA, Blennow O, Duarte RF *et al*. The current management landscape: aspergillosis. *J Antimicrob Chemother* 2016; **71** Suppl 2: ii23–ii29.

9 Clancy CJ, Nguyen MH. Finding the 'missing 50%' of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. *Clin Infect Dis* 2013; **56**: 1284–92.

10 Tissot F, Lamoth F, Hauser PM *et al*. β-Glucan antigenemia anticipates diagnosis of blood culture-negative intraabdominal candidiasis. *Am J Respir Crit Care Med* 2013; **188**: 1100–9.

11 Martinez-Jimenez MC, Munoz P, Valerio M *et al*. *Candida* biomarkers in patients with candidaemia and bacteraemia. *J Antimicrob Chemother* 2015; **70**: 2354–61.

12 Wellinghausen N, Siegel D, Winter J *et al*. Rapid diagnosis of candidaemia by real-time PCR detection of *Candida* DNA in blood samples. *J Med Microbiol* 2009; **58**: 1106–11.

13 Lortholary O, Fernández-Ruiz M, Perfect JR. The current treatment landscape: other fungal diseases (cryptococcosis, fusariosis and mucormycosis). *J Antimicrob Chemother* 2016; **71** Suppl 2: ii31–ii36.

14 Millon L, Herbrecht R, Grenouillet F *et al*. Early diagnosis and monitoring of mucormycosis by detection of circulating DNA in serum: retrospective analysis of 44 cases collected through the French Surveillance Network of Invasive Fungal Infections (RESSIF). *Clin Microbiol Infect* 2015; pii: S1198-743X(15)01032-0.

15 Bassetti M, Peghin M, Timsit J-F. The current treatment landscape: candidiasis. *J Antimicrob Chemother* 2016; **71** Suppl 2: ii13–ii22.

16 Nett JE, Andes DR. Antifungal agents: spectrum of activity, pharmacology, and clinical indications. *Infect Dis Clin North Am* 2016; **30**: 51–83.

17 Agrawal S, Barnes RA, Brüggemann RJ *et al*. The role of the multidisciplinary team in antifungal stewardship. *J Antimicrob Chemother* 2016; **71** Suppl 2: ii37–ii42.

18 Miyazaki T, Kohno S. Current recommendations and importance of antifungal stewardship for the management of invasive candidiasis. *Expert Rev Anti Infect Ther* 2015; **13**: 1171–83.

19 Muñoz P, Valerio M, Vena A, Bouza E. Antifungal stewardship in daily practice and health economic implications. *Mycoses* 2015; **58** Suppl 2: 14–25.

20 Pfaller MA, Castanheira M. Nosocomial candidiasis: antifungal stewardship and the importance of rapid diagnosis. *Med Mycol* 2016; **54**: 1–22.

21 Muñoz P, Bouza E. The current treatment landscape: the need for antifungal stewardship programmes. *J Antimicrob Chemother* 2016; **71** Suppl 2: ii5–ii12.

22 López-Medrano F, San Juan R, Lizasoain M *et al*. A non-compulsory stewardship programme for the management of antifungals in a university-affiliated hospital. *Clin Microbiol Infect* 2013; **19**: 56–61.

23 Standiford HC, Chan S, Tripoli M *et al*. Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. *Infect Control Hosp Epidemiol* 2012; **33**: 338–45.