Rev Iberoam Micol. 2017;34(3):127–129

Revista Iberoamericana de Micología

www.elsevier.es/reviberoammicol

Editorial

Update on the management of intra-abdominal *Candida* infections

Actualización en el manejo de las infecciones intra-abdominales por *Candida*

Eva Calabuig[a,*], Juan J. Camarena[b], Nieves Carbonell[c]

[a] *Unidad de Enfermedades Infecciosas (Área clínica médica), Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[b] *Servicio de Microbiologia, Hospital Universitario Dr. Peset, Universidad de Valencia, Spain*
[c] *Servicio de Medicina Intensiva, Hospital Clínico Universitario, Valencia, Spain*

Invasive candidiasis management has improved in the last decade mainly due to the implementation of a great number of clinical guidelines regarding epidemiology, diagnosis and management of different risk profile patients. Nevertheless, controversial issues still remain, especially concerning intra-abdominal fungal infections in critically ill patients.

Accordingly, Pemán et al.[18] publishes in this number of *Revista Iberoamericana de Micologia* the article *Jávea consensus guidelines for the treatment of Candida peritonitis and other intra-abdominal fungal infections in non-neutropenic critically ill adult patients*. The authors, using a DELPHI methodology in an Spanish region, achieved a total of 36 validated recommendations regarding several aspects of intra-abdominal candidiasis (IAC). The employed methodology is perfectly detailed. From October 2014 until October 2016 authors performed three experts meetings. They aimed to achieve a consensus on the management of peritoneal candidiasis based on the Epico strategy[13] and concluded that these guidelines might help to optimize the management of *Candida* intra-abdominal infections in non-neutropenic ICU patients.

It is interesting to emphasize and put into context some questions about the areas of information presented in these guidelines and, specifically, to highlight some collateral issues that could allow us to gain a better understanding of IAC: (i) epidemiological aspects of temporal and geographic changes in *Candida* spp. distribution; (ii) possible applications of the *Candida* Fluco-R score; (iii) importance of source control as a determining factor in a favorable outcome of IAC, including emergent echinocandin resistance mediated by point mutation within hot spots of FKS genes; (iv) potential extrapolation of candidemia care bundle that could be extrapolated to IAC; and (v) role of antifungal stewardship programs.

From an epidemiological point of view, Pemán et al. have made five recommendations regarding IAC. *Candida* infection epidemiology has changed over recent years, influenced by patient predisposing conditions, local hospital-related factors, and antifungal therapy administered.[5] According to Pemán et al. results, *Candida albicans* remains the most frequent yeast causing intra-abdominal infection, however a shift toward non-*C. albicans Candida* species, such as *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei*, and *Candida lusitaniae* has been observed, some of them having a reduced susceptibility to antifungal drugs. This fact affects critically ill patients with invasive candidiasis or IAC all over the world. Thus, appropriate IAC management should be supported on an updated knowledge of local epidemiology. At the same time, it is necessary a detailed knowledge of antifungal *in vitro* susceptibility among the isolated strains in the hospital.

Previous guidelines[18] identify several risk factors associated with fluconazole resistant *Candida* infections such as pretreatment with systemic triazoles, age >65 years, length of hospital stay >30 days, and gastrointestinal surgery in the 30 days before the previous episode. Another study found that a recent exposure to antibacterial drugs affected the risk for bloodstream infection with *Candida* isolates non-susceptible to fluconazole (Flu-NS).[6] Cuervo et al. developed a simple prediction score to identify Flu-NS candidemia at the bedside.[7] Flu-NS prediction score was studied in 617 cases of candidemia in a cohort extracted from the CANDIPOP study,[20] and in 297 cases of candidemia in a validation cohort from 6 tertiary hospitals in three countries. Hospitalization in a high prevalence unit (HPU) with more than 15% of Flu-NS isolates, prior transplantation, and at least 3 days of prior azole therapy were considered independent predictors of Flu-NS candidemia by multivariate analysis. According to this prediction score, patients could be classified in three groups: (a) low risk patients (score < 1) in whom empirical fluconazole appeared to be a safe initial treatment; (b) patients with several risk factors (score ≥ 2) and a high probability of Flu-NS candidemia (critically ill patients were included in this subgroup), for whom a broad-spectrum therapy should be the first choice, with fluconazole reserved as a step-down option; and (c) those patients with 3 or more points on the Flu-NS score, for whom the use of an echinocandin should be mandatory because of the high risk of Flu-NS isolates. The efficacy and performance of this score should be evaluated in IAC.

Optimization of IAC management also includes early source control. Some recommendations of this guideline enlighten its importance as a determining factor in a favorable outcome of

* Corresponding author.
E-mail address: evacala@yahoo.com.ar (E. Calabuig).

http://dx.doi.org/10.1016/j.riam.2017.02.005

IAC, including peritonitis, abdominal abscess, and gastrointestinal perforation or anastomotic leak. Usually this measure on focus infection is positioned at the same level of importance than prompt and appropriate antifungal therapy in previous studies. In fact, Kollef et al.[10] demonstrated in a retrospective cohort study of septic shock patients with positive blood cultures for *Candida* species that delayed antifungal treatment and failure to achieve timely source control were independently associated with a greater risk of hospital mortality (97% *vs.* 52%, $p < 0.001$). Gastrointestinal focus represented 12% of all the infection sources described in this study. Similarly, Aguilar et al.[1] described in a single center study of surgical critically ill patients a 100% survival rate in IAC patients, percentage that can be explained by an early antifungal therapy and an adequate source control.

To this extent, the recently published American guidelines for the management of candidiasis[17] emphasize that the treatment of IAC should include source control, with appropriate drainage and/or debridement, and that adequacy of source control and clinical response would determine the duration of therapy. However applying both measures, early echinocandin prescription (guided by the *Candida* species isolated and knowledge of the local epidemiology) and source control, could involve some risks in our daily clinical practice.

As a matter of concern, the emergence of co-resistance to both azoles and echinocandins in clinical isolates of *C. glabrata*, a species that appears to be unique in its ability to sequentially acquire and express resistance mutations, has been documented over time.[19] Do we will also need a score to determine the risk of resistance to echinocandins?

Pemán et al. conclude that patients with a peritoneal candidiasis episode should be treated with an echinocandin if they are hemodynamically unstable, if an azole therapy has been previously used or if a fluconazole-resistant *Candida* species was isolated in the peritoneal fluid obtained by means of a surgical procedure (l00% of consensus).[18] Authors also explain that the susceptibility patterns to antifungal agents vary depending on the *Candida* species (i.e. *C. glabrata* is generally dose-dependent or resistant to azoles, and *C. krusei* is intrinsically azole resistant). However, no mention to echinocandin resistance, an emergent problem over the recent years, has been made. Echinocandin resistance has been found in most of the *Candida* species with clinical relevance, but it is particularly common in *C. glabrata* with rates exceeding 10% in certain institutions.[3] Echinocandins act through non-competitive inhibition of 1,3-β-D-glucan synthase, an enzyme encoded by FSK genes that is responsible for the biosynthesis of a major cell wall glucan polymer. Acquired echinocandin resistance, among species that are normally susceptible, has been reported in *C. albicans*, *Candida dubliniensis*, *Candida kefyr*, *C. glabrata*, *C. krusei*, *C. lusitaniae* and *C. tropicalis* with mutations in specific hot spot regions of the FSK1 gen for all *Candida* species and, additionally, FSK2 in *C. glabrata*. Pemán et al. explain how IAC has recently been described as a hidden reservoir of echinocandin-resistant *Candida* species.[23] FSK *Candida* mutants have been isolated from 24% of abdominal candidiasis exposed to echinocandin. *C. glabrata* (29%) and *C. albicans* (14%) resistant to echinocandins were identified and also significantly associated with prolonged echinocandin exposure, breakthrough infections and therapeutic failures despite source control interventions. Thus we consider that the identification of the isolate and determining its antifungal susceptibility are essential to optimize candidiasis treatment, not only to perform a de-escalation to fluconazole as Pemán et al. propose, but also for the control of echinocandin resistant strains.

The present IAC guidelines do not mention the recent advances in candidemia care bundle strategy.[2,25] However, we do believe that this approach could be adapted to IAC management while waiting for its own key components. IAC is the predominant type of invasive candidiasis after candidemia and special efforts have been recently made to standardize its diagnostic criteria. In this sense, critically ill patients with complicated IAC would probably benefit in a similar way from the application of the above mentioned comprehensive care bundle. Sepsis care bundles application have shown better compliance and results than the implementation of individual measures.[4,8,11]

Based on these results, antifungal stewardship teams have proposed a bundle approach to improve the care of patients with candidemia. The first study that analyzed the impact of a care bundle on the management of candidemia followed the 2009 American Guidelines and included: (i) appropriate antifungal therapy based on culture and susceptibility results within the first 72 h; (ii) removal of intravascular catheters; (iii) perform of new blood cultures at least every 48 h until clearance of candidemia; (iv) appropriate duration of antifungal treatment defined as 14 days after the first negative blood culture, or at least four weeks for documented disseminated disease; and (v) ophthalmologic examination to evaluate *Candida* endophthalmitis except in neutropenic patients in whom the procedure should be performed after the neutropenia is solved. In case of persistently positive blood cultures >72 h, or presence of prosthetic heart valve, vascular graft or implantable pacemaker or defibrillator as possible metastatic foci, additional testing (i.e. transthoracic or transesophageal echocardiography) and special monitoring by the infectious disease team is recommended. This was a quasi-experimental study that demonstrated an improvement on the management of patients with candidemia, although was unable to detect a significant difference in mortality. Afterwards, in a bigger sample size study based on a Japanese database, the Mycoses Forum in Japan published the Appropriate Candidal Treatment Implementation of Non-neutropenic strategies (ACTIONs) bundles for invasive candidiasis, with a compliance rate of 21%.[25] It consisted of nine items, five of them being equal to those previously described. The four different items added in this study were (vi) initial appropriate dosing of antifungals; (vii) assessment of clinical efficacy on the third to fifth day in order to consider an alternative therapy, if necessary; (viii) appropriate choice of alternative antifungals; and (ix) oral step-down therapy for patients with favorable clinical course. When the last item was excluded, compliance with the bundles was revealed to be an independent predictor of clinical success (resolution of all attributable signs and symptoms associated with candidemia) and 28-day mortality.

Despite other individual elements of care bundle have been identified as relevant, probably a more vigorous and special promotion of ophthalmological examination should be carried out. In a prospective multicenter trial with 370 non-neutropenic patients (40% admitted due to abdominal surgery), Oude Lashof A et al. evaluated different systemic antifungals for the treatment of ocular manifestations of candidemia, and they found an incidence of 16% for metastatic ocular infection.[16] Therapy with either voriconazole or amphotericin B followed by fluconazole was successful in 65% of cases. None of the cases of *Candida* chorioretinitis progressed to endophthalmitis during the systemic treatment, being the last one uncommon (1.6%). Based on this study, in which the baseline fundoscopy was negative and new lesions were detected at follow-up in nearly 20% of cases, dilated fundoscopy should be performed at least 1 week after the onset of therapy to increase its sensibility to detect ocular lesions. Authors suggested switching to voriconazol or amphotericin B in those ocular affected patients initially treated with echinocandins due to their poor ocular penetration. It seems that ocular candidiasis is asymptomatic, and despite early hematogenous inoculation, the lesions require some time to evolve. Subsequent explorations are necessary to guide antifungal treatment duration until ocular lesions are resolved.

Besides a high cost, the use of antifungal agents is associated to well known toxicities, and the promotion of resistant and emerging fungal infections. Therefore antifungal stewardship (AFS) programs are essential to avoid unnecessary treatments, to adjust treatment duration, to watch over adverse effects and to upgrade de-escalation.[14] AFS programs have a vast potential to improve the quality of care and the safety of patients. However, AFS has received very little attention in comparison with antibiotic stewardship programs.

The most frequent causes to modify an antifungal treatment that appear in different AFS programs are inadequate antifungal coverage, no confirmed infection, combined treatment not indicated or oral route indicated.[15,21,22] We should remark that in intra-abdominal fungal infections, blood biomarkers cannot help to establish a decision on the step-down antifungal therapy, complicating even more this task.

On the other hand, AFS programs conducted to date have improved the quality of care of patients with proven invasive fungal disease but a reduction in mortality has not been achieved.[15,22] Furthermore, any effect on resistance rates has been demonstrated.[12] Swoboda et al. performed a study with an off-label use of posaconazole for *C. glabrata* and *C. krusei* infections when enteral absorption was certain and the patient was stable in a German surgical ICU. The intervention resulted in a 50% reduction in the costs of antifungal agents, with no changes in outcome measures.[24] Another study about a caspofungin stewardship program reported from ICUs in a USA hospital showed a significantly decreased median duration of therapy (4 *vs.* 2 days, $p = 0.001$) and was more effective in the medical ICU than in the surgical ICU. The potential cost saving per patient was $1013.[9]

In the future, AFS programs will be likely to make use of electronic decision trees and automatic instructions; however, the opinion of the physician will always be key to ensure a high standard of medical practice, taking into consideration the individual characteristics and presentation of each patient with *Candida* infection. Medical institutions need to provide human and financial support to enable AFS teams to achieve better results, and it is essential to sensitize, train and increase the clinicians, pharmacists and clinical microbiology specialists awareness. A cultural change among healthcare providers and authorities is currently needed to improve antifungal use worldwide.

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