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Conference report from the International Congress on Infectious Diseases 2014: part one

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ABSTRACT The 16th International Congress on Infectious Diseases (ICID) was held in Cape Town this year, marking the return of the conference to Africa for the first time in 22 years. While infectious diseases such as malaria, tuberculosis and HIV – all still prevalent in the African healthcare landscape – dominated the program, the conference featured several important sessions on fungal infection and a significant number of posters devoted to this critical medical area. Within the context of the rise of antimicrobial resistance, now identified by the WHO as one of the three greatest threats to human health, came the message that resistance is not limited to antimicrobials, but that antifungal resistance is also a significant and emerging threat worldwide.

Causes of antifungal resistance

Antifungal resistance may be intrinsic or acquired in *Candida* and *Aspergillus*, with acquired being less common than intrinsic, possibly due to the fact that fungi do not exchange resistance genes via plasmids. It may be present in drug-naïve as well as antifungal drug-exposed patients [1]. Prior antifungal treatment confers a selection pressure and raises the awareness of possible resistance in patients failing therapy, thus calling for susceptibility testing.

Speaking at the Fungal Infections Symposium on the topic of ‘Tracking resistance to antifungal drugs for *Candida* spp.’, Jennifer Coetzee (Johannesburg, South Africa) confirmed a need for regular surveillance studies in the management of antifungal resistance and highlighted the various factors attributed to the cause of resistance. Coetzee noted prophylactic use of antifungal agents and the observation that underdosing azoles such as fluconazole and voriconazole can result in acquired resistance as well as the increased use of antifungals. Unexpected factors such as the agricultural use of azole fungicides, first seen with azole-resistant *Aspergillus* in the Netherlands [2,3] and now worldwide, should not be underestimated, as these too play a role in driving resistance.

Prevalence of antifungal disease

Serious fungal infections affect approximately 300 million people each year and result in over 1,350,000 deaths, a greater number than those attributable to tuberculosis or malaria [4]. Presenting at the conference, Francesco Menichetti (Pisa, Italy) [5] stated that *Candida* spp. are an important cause of bloodstream infection and are associated with a high morbidity and mortality rate [6]. He attributed this increasing incidence to the intricacy of medical and surgical procedures which occur in the critically ill patient.

KEYWORDS

- antifungal resistance
- antifungal treatment
- *Aspergillus* • *Candida*
- fungal infection • ICID
- infectious disease
- prophylaxis

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Menichetti proceeded to present results of a recent 3-year survey conducted in Italy and Spain [7]. The survey demonstrated the overall incidence was 1.55 cases per 1000 admissions. *Candida albicans* was the leading agent of infection (58.4%), and the majority of candidemia episodes were found in the internal medicine department (49.6%) followed by the surgical ward, the intensive care unit (ICU) and the hemato-oncology ward. Out of the 955 episodes of candidemia identified as eligible for evaluation, 381 of the patients (39.9%) died within 30 days from the onset of candidemia [7]. In terms of species of *Candida*, a shift toward non-*albicans* species has recently been reported, particularly in hematological, transplanted and ICU patients and the data presented by Menichetti confirmed this with *C. parapsilosis*, *C. tropicalis* and *C. glabrata* being among the *Candida* species isolated (incidences of 19.5, 9.3 and 8.3%, respectively). Of concern was the trend toward reduced antifungal susceptibility in this non-*albicans* *Candida* species. Around 5% of all tested isolates (n = 995) were resistant or susceptible dose dependent to fluconazole. In these patients, as well as those with *Candida* species, the intrinsic and emerging resistance to azoles represents a major challenge for empirical therapeutic and prophylactic strategies.

Management of fungal disease within the context of antifungal resistance

The accurate speciation of *Candida* isolates is a key factor in determining empiric choice of antifungal. However, to make a definitive diagnosis of invasive *Candida* is very difficult. While blood cultures are essential, they are not very useful in the initial stages, according to Coetzee who presented South African data from the Ampath National Reference Laboratory. In 262 individual episodes of candidemia, the time to positivity was a median of 59 h. In addition, sensitivity was not good (about 50–70%) and Coetzee noted the challenge of identifying the remaining 30%. β -D-Glucan is one adjunctive therapy that may be helpful and, in the future, PCR testing will present as a useful modality.

Coetzee recommended that in the management of invasive fungal infections, regular surveillance studies to track distribution and susceptibility patterns will provide guidance regarding empiric therapy [8]. When evaluating resistance or surveillance data, Coetzee stated that two things must be considered critical: the

criteria and the methodology used. With regards to the criteria used to interpret the results of the susceptibility data, one must be aware that differences exist between Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints. CLSI published new breakpoints in January 2013 which have had a significant effect on the interpretive categorization of certain drugs, and this resulted in major differences to certain species, especially *C. glabrata*. The method of surveillance testing [9] should be carefully noted due to the fact that certain commercial antifungal susceptibility testing systems may be associated with a significant misclassification of some species/antifungal combinations.

Coetzee concluded that when making decisions regarding empiric therapy in the context of emerging antifungal resistance, the most important factor for clinicians to be aware of is the epidemiology and sensitivity testing results in their own units. To this point, regular surveillance needs to be done to guide empiric therapy.

Speaking on the need for early empiric therapy in invasive fungal infections in the ICU setting, Eckhard Müller (Herne, Germany) [10] emphasized that antifungal therapy must be started in a timely manner as the delay in initiating antifungal treatment is associated with a significant and independent determinant of hospital mortality [11]. In addition, non-*albicans* *Candida* are increasingly documented [12]. A poster presentation confirmed this point – of 31 *Candida* blood stream infection (BSI) isolates, 27 (87.10%) were non-*Candida albicans* (NCA) species, indicating various resistance rates to antifungal drugs [12]. Data presented by Müller confirmed NCA presence as being increasingly documented, with isolates exhibiting resistance or SDD to fluconazole. He continued that this leads to consideration of an echinocandin as a rational choice and alternative therapeutic option to fluconazole for treating invasive candidemia, in the noncritically ill as well as being first choice in ICU patients. Müller cautioned, however, that not all echinocandins are equally effective, particularly when it comes to non-*albicans* *Candida* infections. He concluded that the following axiom should guide empiric therapy for invasive fungal infection treatment to optimize therapy and minimize the potential for resistance: treat early, with the right drug for the right patient, at the right dose.

Standards to guide prophylaxis

The epidemiology of invasive fungal infection in severely immunocompromised hosts has evolved into a complex scene and now includes many NCA species and invasive molds such as *Aspergillus*. Dimitrios Kontoyiannis (TX, USA) [13] spoke on standards in prophylaxis in this high risk group. He highlighted that patients in ICU who are immunocompromised and critically ill, represent an increasing population at risk for invasive pulmonary aspergillosis [14]. Institution-specific epidemiologic data remains key for this population, together with refinement of risk stratification and risk/benefit analysis.

Kontoyiannis went on to note that stratification of invasive fungal infection risk could be improved based on emerging genetic, metabolic risk factors. Cooperation and a multidisciplinary approach among the medical team involved in patient care is critical, enabling a decision to be taken as to whether the risk of a life-threatening invasive fungal infection outweighs the risk of toxic effects and drug interactions introduced by the antifungal agent used.

When deciding which drug to prescribe, spectrum alone is not the only factor that matters

in this patient group. There are broad-spectrum antifungals: amphotericin B parenterally is good, and the new-generation azoles, posaconazole and voriconazole, provide excellent coverage. However, Kontoyiannis noted that pharmacokinetic limitations must be acknowledged. Drug–drug interactions, toxicity and affordability are all factors which need to be considered to optimize prophylaxis. Kontoyiannis concluded by saying that personalized decisions and reliance on institution-specific epidemiologic data are expected to continue to be a major part of the ‘art and science’ of prophylaxis for fungal infections in severely immunocompromised hosts.

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