Update on Antifungal Resistance in Children: Epidemiology and Recommendations

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Knowledge of the (local) epidemiology of invasive fungal infections in children is important with respect to the development of management strategies. In addition to species-specific activity of antifungals, in some clinical settings and geographic regions acquired resistance is becoming a clinically relevant problem. Microbiological resistance relates to an in vitro susceptibility test, which indicates that the activity of a certain drug against the pathogen is low or absent and corresponds with a high probability of treatment failure. Clinical resistance, however, is when a patient fails to respond to antifungal therapy, which might be due to microbiological resistance of the pathogen but could also be caused by other factors. Management of antifungal drug-resistant invasive fungal disease is challenging with respect to detection of resistance and the treatment regimen.

Antifungal Resistance Among Candida spp

Candida krusei is inherently resistant to fluconazole, whereas Candida glabrata has variable susceptibility to fluconazole, and treatment with fluconazole for infections caused by these species is not advised. Concern has risen with regards to the susceptibility of Candida parapsilosis to the echinocandins. Response rates to fluconazole compared with anidulafungin were shown to be different per Candida spp. Although favorable outcome was reported with anidulafungin for Candida albicans, Candida tropicalis and C. glabrata compared with fluconazole, the opposite was true for C. parapsilosis. Due to the fact that C. parapsilosis is the most or second most reported species in the pediatric population, the use of the echinocandins is of concern. In vitro susceptibility testing of pediatric C. parapsilosis isolates reports the highest minimal inhibitory concentrations for micafungin and caspofungin, although comparable to those found in isolates recovered from adults.

Recent data derived from the SENTRY Antimicrobial Surveillance Program show clear differences in Candida spp distribution causing bloodstream infections according to patient age and the associated susceptibility patterns. Dominant causes of candidemia in the pediatric age group (0–19 years) were C. albicans (30%), C. parapsilosis (28.5%) and C. tropicalis (12.9%), with very few infections due to C. glabrata (2%) and C. krusei (0.8%). Compared with the adult age groups, the prevalence of C. parapsilosis and C. tropicalis was the highest in the pediatric age group, whereas C. glabrata and C. krusei were substantially more frequently isolated from adults with candidemia. Susceptibility testing showed clearly that no resistance was present to fluconazole, voriconazole and posaconazole and the 3 echinocandins among the isolates recovered from pediatric patients, with the exception of C. krusei being inherently resistant to fluconazole. Resistance to azoles and echinocandins was most prominent among isolates of C. glabrata in the adult age groups. Resistance to echinocandins among C. parapsilosis isolates recovered from adult patients was not observed, but up to 16% showed to be resistant to fluconazole.

A prospective multicentre Spanish surveillance study investigated 203 episodes of candidemia in 200 children. C. parapsilosis was the leading species (46.8%) followed by C. albicans (36.5%), C. glabrata (3.6%) and C. krusei (1%) were infrequent causes of fungemia. All C. parapsilosis isolates (n = 95) were susceptible to echinocandins except 1 isolate, which was micafungin resistant. Resistance to azoles and/or echinocandins was observed in 2 of 74 (2.7%) C. albicans isolates and 2 of 12 (16.7%) C. tropicalis isolates. The susceptibility rate to fluconazole was 99.4% for C. albicans and C. parapsilosis.

Non-albicans Candida spp (56%) were also the predominant cause of candidemia in the prospective multicentre international study performed by the Fungal Pediatric Network including 15 US and 9 international sites. In this study, outcome could be related to the causative species and treatment given. Most pediatric patients (196 children and 25 neonates) with invasive candidiasis had a successful outcome, although neonates did better compared with older children (92% versus 76%). Death occurred in 19% and 8% of children and neonates, respectively. The most commonly used agent for neonatal candidiasis was fluconazole (32%), followed by caspofungin (24%), liposomal amphotericin B (16%) and micafungin (8%). In pediatric patients, the azoles were used more frequently (30%), followed by echinocandins (25%) and fluconazole (21%). Similar response rates occurred both in neonates and older children treated with polyenes, azoles and echinocandins. Lack of activity of the most commonly used antifungal agents, fluconazole and the echinocandins, appeared not to play a prominent role in treatment failure.

The European Society for Clinical Microbiology and Infectious Diseases has recently published a guideline for the management of invasive Candida diseases in neonates and children. In neonates, appropriate agents for the treatment of invasive candidiasis include amphotericin B deoxycholate (BII), liposomal amphotericin B (BIII), amphotericin B lipid-complex (CII), fluconazole (BII), micafungin (BII) and caspofungin (CII). Treatment recommendations for children with invasive candidiasis were largely extrapolated from adult studies: the echinocandines are considered primary treatment options (caspofungin [AI], micafungin [AI] and anidulafungin [BII]), whereas liposomal amphotericin B (AI) is an alternative primary treatment option. Another guideline that has been made public, but remains to be published, is the guideline of the European Conference on Infections in Leukemia. At the 4th European Conference on Infections in Leukemia meeting, a pediatric expert group made recommendations for the management of invasive fungal disease in patients with hematological malignancy. For the treatment of invasive candidiasis caspofungin, fluconazole, liposomal amphotericin B, micafungin and voriconazole are recommended (BII).

As C. glabrata and C. krusei are very infrequent in the pediatric setting, fluconazole remains an option for candidemia treatment while awaiting species identification, except in children with prior azole exposure, which is recommended by the latest Infectious Diseases Society of America guideline. Echinocandins are an attractive alternative based on efficacy data and safety profile in adults and in pediatric candidemia. However, reports of
increased prevalence of candidemia due to C. parapsilosis in the current echinocandin era and breakthrough infections due to C. parapsilosis in patients treated with echinocandins are worrying. Therefore, the Infectious Diseases Society of America recommends to use either a lipid formulation of amphoterin B or fluconazole in the treatment of invasive infections caused by C. parapsilosis.8

Azole Resistance in Aspergillus fumigatus

Acquired resistance to azoles is an emerging problem in A. fumigatus. Patients might develop azole resistance during therapy. This has been reported almost exclusively in patients with chronic Aspergillus disease that is characterized by cavitary lesions.10 Apparently the combination of growth of A. fumigatus in a cavity, such as an aspergilloma, and azole exposure enables selection of azole-resistant traits.11 Patients with azole-resistant Aspergillus disease were reported to frequently fail azole therapy.11 Such chronic Aspergillus diseases are uncommon in pediatric patients, and although resistance may complicate the treatment of individual patients, there is no apparent risk of spread of azole-resistant isolates to other patients.

A second route of resistance selection has been suggested, where A. fumigatus has become resistant through exposure to azole fungicides in the environment.11 Azole fungicides are abundantly used for crop protection and material preservation. A. fumigatus, which is a saprophytic fungus, is believed to become resistant in the environment through exposure to azole fungicides that exhibit activity against this species.12 Five azole fungicides were identified with a molecule structure that is highly similar to that of the medical triazoles.13 A. fumigatus may develop resistance mechanisms against these azole fungicides and, due to the molecule similarity, the medical triazoles are inactive as well.

The environmental route of resistance development has major consequences as azole-resistant Aspergillus disease may develop in both azole-treated and azole-naïve patients, and the full spectrum of Aspergillus diseases may be encountered. Breakthrough azole-resistant invasive aspergillosis was reported in pediatric patients with chronic granulomatous disease while receiving itraconazole prophylaxis14 and in a 10-year-old boy with high-risk acute lymphoblastic leukemia treated with hematopoietic stem-cell transplantation during voriconazole therapy.15 Central nervous system aspergillosis due to an azole-resistant A. fumigatus isolate was reported in a 11-year-old girl with precursor B cell lymphoblastic lymphoma.16 She died as the cerebral lesions progressed despite liposomal amphotericin B and caspofungin combination therapy. Overall, patients with azole-resistant invasive aspergillosis commonly failed to azole therapy, with a 12-week mortality rate of 88%.17

There are currently no treatment recommendations for azole-resistant Aspergillus disease, although azole monotherapy appears to be associated with a high probability of failure. Experimental models of infection indicate that the combination of voriconazole with anidulafungin may be synergistic in azole-susceptible infection, but that synergy is lost in mice infected with a voriconazole-resistant isolate.18 There is concern that in isolates that are highly resistant to voriconazole, the efficacy of the combination may rely solely on that of the echinocandin, which is suboptimal. Liposomal amphoterin B was shown to be effective against azole-resistant A. fumigatus isolates irrespective of the azole resistance mechanism.

The prevalence of azole resistance varies depending on the geography and the patient group. Azole resistance was found to be widespread in the Netherlands and is increasingly being reported in other European countries including Belgium, France, Spain, Denmark, Italy, Austria, Germany and the United Kingdom. In most azole-resistant isolates a specific Cyp51A gene–mediated resistance mechanism was reported (TR/L98H) both in clinical and environmental isolates. The geographic area where TR/L98H is reported coincides with the region with the most intensive use of fungicides. Azole resistance, due to the TR/L98H resistance mechanism, was also reported in clinical A. fumigatus isolates from China and India. To date TR/L98H has not been reported in North America.

In the management of invasive fungal diseases in children and neonates, still many research gaps remain. The publication of treatment guidelines helps pediatricians to make evidence-based choices in the management of invasive fungal diseases in children at risk. However, the evolving epidemiology of resistance underscores the continued need for research and surveillance in order to provide the best possible care for children with fungal diseases.

REFERENCES

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