Invasive fungal infections

Numerous fungal species exist globally, with nearly 500 species known to infect humans. Fungi are ubiquitous and exist in the environment or may be part of the normal flora in humans and animals. In humans, fungal infections are of varied severity, including mild, superinfection of the skin, severe and/or life-threatening invasive disease, especially in immunocompromised patients.[1] Generally fungal infections are classified according to the site of infection, such as superficial, cutaneous/mucosal, subcutaneous and invasive. Invasive fungal infections (IFI) occur when fungi are isolated from blood, other sterile sites and tissue showing invasion into specific organs. Characteristically, IFI are serious, deep sited, disseminated and commonly systemic. Following an episode of fungal infection, factors such as fungal pathogenicity, host immune response and site of infection are major contributing factors that affect the outcome of the episode.[1-3]

In children, IFI contribute significantly to morbidity and mortality, especially in those immunocompromised or admitted to critical care units with indwelling catheters. The last three decades saw a significant rise in the burden of IFI due to the HIV pandemic, the high number of children on immunosuppressant therapy for cancers or as transplant recipients, and many critically ill children requiring endotracheal tubes, central lines and urethral catheters.[3,4] Specific groups of children also at risk of an IFI include premature infants, cancer or transplant patients on immunosuppressant therapy with or without neutropenia, burns patients, patients on prolonged antibiotic therapy, and patients with congenital or acquired immunodeficiencies. Predominantly, IFI are caused by three fungi: *Candida* spp., *Aspergillus* spp. and *Cryptococcus* spp. Together, IFI caused by *Candida*, *Aspergillus* and *Cryptococcus* spp. contribute to nearly 1.5 million deaths globally yearly.[4,5]

In this issue of *AJTCCM*, Hlophe and colleagues[6] share their data from a retrospective study on IFI in children <12 years admitted to the paediatric intensive care unit (PICU) of a tertiary hospital over a 2-year period in Durban, South Africa. They noted an incidence of IFI of 35/1 000 children. Significantly, most of the children were <12 months old. All of those with IFI had received antibiotics and nearly all of them had a urethral catheter in situ. The majority of the children with IFI had endotracheal intubation and two-thirds had central venous catheters. Presence of IFI contributed significantly to mortality, as well as prolonging the duration of PICU stay compared with children admitted with bacterial infections. The leading fungal pathogen was *Candida* spp. with *C. albicans* being most commonly isolated; the others were unspeciated *Candida*.

Invasive candidiasis (IC) is more common in young children and neonates and it accounts for nearly 40 - 75% of all IFI. In children, the leading *Candida* sp. causing IC is *C. albicans,* accounting for up to 53% of all cases. Other *Candida* spp. less frequently isolated include *C. parapsilosis* (21%) and *C. tropicalis* (10%). Infrequently *C. glabrata* and *C. krusei* are isolated in children.[7,8] *Candida* spp. are found predominantly on the skin, mucosal surfaces, and in the gut as commensals. Infections caused by *Candida* include thrush, vaginal and IC or disseminated candidiasis (DC). IC is a serious infection, and in children the lungs, kidney, heart and brain are more frequently affected. It is life-threatening and responsible for significant mortality rates up to 40% in immunocompromised patients.[5] The risk factors for candidaemia are presence of central lines, neutropenia, immunosuppressant therapy and neonates with low gestational age. Neonatal candidiasis risk is much higher when the birthweight is lower – in up to 15% of neonates.[9]

Invasive aspergillosis (IA) caused by *Aspergillus fumigatus* is also an important cause of IFI. It is a saprophytic fungus which causes about 200 000 cases of IA yearly, contributing significantly to mortality in nearly 30 - 95% of cases of IA. Lastly, invasive *Cryptococcus* caused by *Cryptococcus neoformans* and *Crypytoccocus gati* spp. affects over a million individuals and causes mortality in up to 20 - 70% of cases.[5,10]

In the diagnosis of IFI, early recognition and prompt institution of appropriate treatment is fundamental for management to be successful. The ideal diagnostic method should be able to diagnose the infecting fungi at the species level and provide information on drug resistance patterns. This is necessary as there is such a wide fungal diversity in high-risk patients and there are differences in effectiveness of antifungal agents for specific fungi. Most importantly, there is increasing resistance among fungal pathogens. In mycological diagnosis, microscopy and culture remain the gold standard. The major challenges that exist are the difficulty in obtaining samples that are appropriate and sufficient in quantity, as well as the prolonged culturing time of the fungi.[11]

More recently, newer methods used to diagnose IFI can detect the circulating fungal cell wall component or DNA component of the fungi in blood or some other body fluids. In addition, beta-D-glucan assay may also be used for fungal diagnosis in children. Most opportunistic fungi have beta-D-glucan, thus making the test species nonspecific. However, it is highly sensitive at detecting invasive fungal pathogens although false-positive results may also occur. In neonates, beta-D-glucan can help in diagnosis of IC. The use of beta-D-glucan needs to be continually evaluated and validated in children. Lastly, imaging also has a role in the diagnosis of paediatric IFI despite the major concern of radiation exposure in children with regard to high-resolution computed tomography (HRCT) scans.[12,13]

Generally, agents used in the management of IC include amphotericin B and fluconazole, which are much older agents, and newer agents such as capsofungin and mucofungin.[14] Patients requiring treatment for IFI must have complete evaluation of their clinical status, organ function and type of *Candida* sp. causing IC as well as its resistance patterns. Treatment outcomes depend on the time of diagnosis to time of initiating appropriate antifungal chemotherapy. Patients with indwelling catheters must have them removed. Immunosuppressant drugs such as steroids should be readjusted or replaced. The duration of IC treatment is usually 2 weeks after the clearance of the species in the blood and improvement of symptoms.[14-16]

In IA, antifungal therapy may be initiated based on the risk profile of the patient, and clinical, laboratory and imaging findings. Despite this, microbial diagnosis is superior and continuous efforts must be made to isolate the specific *Aspergillus* sp.

Mortality following IFI is high, and other severe complications such as neurodevelopmental delay may occur, especially in neonates.

Efforts at preventing IFI must be sustained, such as cautious use of antibiotics and steroids, promoting hygienic measures in the intensive care unit and encouraging breastfeeding as well.[17,18]

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