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Review Article

Invasive Fungal Infections in Children with Hematological Malignancy

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Abstract:

Invasive fungal infections (IFI) are a major cause of morbidity and mortality in patients with haematolgical malignancies. Factors that appear to be associated with IFIs in both children and adults in this severely immunosuppressed population are the underlying malignancies, presence of profound and long lasting neutropenia, high intensity of the therapeutic regimens, hematopoietic stem cell transplantation and previous antibiotic therapy. In patients with hematological malignancy most invasive fungal infections are caused by Candida and Aspergillous species. Though the incidence of IFI in adult may be as high as 30 % and the mortality up to 50 %, the true incidence in children and its outcome are more difficult to assess because of the growing trends towards more invasive chemotherapeutic regimens, the development and introduction of new antifungal drugs and prophylactic antifungal strategies and difference in design and patient populations among the various studies. In general the incidence rate in children appears to be lower than in adults. The diagnosis are based on the basis of microbiological and radioimagings with the criteria defined by the EORTC/MSG. Caspofungin, Liposomal amphotericin B and Voriconazole are often the first line empirical antifungal agents

Keywords: *Invasive Fungal Infections (IFI).*

Introduction:

Invasive Fungal Infections(IFI) are still a major cause of morbidity and mortality in patients with hematological malignancies despite improvement in the diagnosis and treatment modalities.[1,2] Factors such as neutropenia, damaged mucosa, receiving high dose chemotherapy, undergoing invasive medical procedures and using broad spectrum antibacterial drugs constitute the risk factors for IFI.[3-6] In children the true incidence and outcome of IFI are more difficult to determine because of growing trend towards more invasive chemotherapy schedule, the development and introduction of new antifungal drugs, prophylactic Use of antifungal agents and difference in design and patient populations in various studies.[6] The mortality rate in IFI in non immunecompromised children hospitalized in the paediatric intensive care is 32 % compared to children with hematological disease displaying the mortality rate of approximately 60 %. The mortality rate related to invasive fungal infection in children with hematological disorders were 30 %.[6,7]

The most common fungi causing invasive infections in hematological malignancies are Aspergillus species and Candida albicans but non albicans Candida and a growing number of other organisms like Zygomycetes, Trichospiron, Fusarium species are increasingly identified now a days.[8,9]

The clinical symptoms and radiological patterns are often nonspecific and delayed diagnosis often lead to delayed therapy and poor outcome.[9] Examination commonly includes a direct smear, culture and histological analysis but in some cases this is really challenging as it requires invasive procedures A non invasive procedure like RT-PCR can be a suitable options for clinical samples in early diagnosis.[9-11] Currently four classes of antifungal agents are used

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in the treatment in IFI. They are Azoles, Polynes, pyrimidine analogue and Echinocondrin.[12] Monotherapy is often preferred for the treatment of fungal infection in paediatric patients. In paediatric patients Caspofungin and liposomal Amphotericin B are now a days often the first line empirical agents along with Voriconazole.[13] So this review tries to address this very complex issue of IFI which is a very important entity in Hematological malignancies in children like ALL, AML, Hodgkin and Non Hodgkin Lymphoma.

Epidemiology:

There are wide variations in the epidemiology regarding Invasive fungal infections and more so as the paediatric studies are relatively limited.

Badiee et al. showed in a study the female to male ratio to be 38:48 and the mean age of the patients was 6 years in children with IFI. The most common hematological disorder in these patients were ALL in 50 patients (55%), AML in 21 patients (24%) followed by Hodgkin Lymphoma and Burkitt's Lymphoma and a total of 225 specimens consisting of Blood, Urine, Cerobrospinal fluid, Pleural and ascitic fluid, Bronchoalveolar lavage, Abscess secretion and abdominal tap were examined for fungal infections. The rate of IFI among paediatric patients with hematological disorder were found to be 16.3 %. They consisted of proven and probable IFI.[14] In an adult study by Livio Pagano et al. the commonest hematological malignancies with IFI were Acute Leukaemia (ALL and AML), followed by chronic Leukaemia, NHL and Hodgkin Lymphoma. There were 1538 proven or probable IFI (4.6%), Over half were caused by molds (2.9%).[2]

Markantonatu et al. had found Candida, Aspergillosis, Mucormycosis in15-17, 17-18, 4 cases in Greek children with malignancy.[15] Baytan et al. also found 23 patients 14.3%) with IFI in their study. Ten children had proven and 13 children had probable IFI with F/M: 12/11. The mean age was 7.8 ± 3.5 yrs.[8] Mor et al. had 75 of the 1047 patients (7.2%) with a diagnosis of IFI. Proven, probable and possible were 21.3, 23 and 54.7 % respectively.[6] One point four percent (1.4 %) of all patients had yeast infection and 5.7 % had mold infections. Highest number of IFI were found in ALL and AML Patients over a period of 9 years. Hovi et al. only found 2 out of 98 children with IFI.[16] In 27 out of 117 episodes of clinical suspicion of IFI and the rate was quite low. Bartlett et al. in a retrospective data of 10 years found 337 IFI episodes in 330 children with malignancies. The median age was 8.4 yrs. Of them 149 were proven, 51 probable and 110 possible IFI episodes. They were mostly ALL and AML followed by Lymphoma.[17] Calton et al. in a UK study showed fungal isolates to be 7.1 % and predominantly they were Candida species.[18]

Kurosawa et al. also in their study analyzed 2821 patients with hematological malignancies, documented proven and probable IFI were diagnosed in 38 patients, the rate being 1.3%, 18 patients had proven IFI and 20 patients had probable IFI.[1] According to EORTC consensus criteria among 38 patients with IFI 19 underwent Allogenic HSCT, one underwent autologous HSCT and 18 underwent for chemotherapy alone. The incidence of IFI was 5.4 % in Allogenic HSCT patients, 4 % in Autologous HSCT patients and 4.8 % underwent chemotherapy alone. In 38 patients with IFI, Proven IFI Candida (n=6), Mucor (n=6), Aspergillous (n=3), Trichosporon (n=2), and Geotricha (n=1) were the causative pathogens. Nineteen of 20 patients with probable Aspergillosis were diagnosed by Lung CT scan or Brain MRI and positivity of GM assay. Among 23 cases of Aspergillosis 22 cases were GM positive but only 9 out of 23 cases were BDG positive. Among 6 cases of Mucormycosis three cases were diagnosed by Autopsy. A study by Wang et al. in Australian children showed 348 episodes of IFI in 331 children.[19] Of these, 149 episodes occurred in 142 children with Acute lymphoblastic leukaemia. Twenty six episodes of IFI occurred in children who had undergone HSCT for ALL. Ninety four IFI episodes occurred in 94 patients with primary non relapsed disease and 29 episodes occurred in 25 patients with refractory disease. Overall a proven, probable and possible IFI was diagnosed in 56, 22 and 39 episodes respectively. The prevalence of IFI in children with ALL is reported to range between 4 and 35 % depending on era, chemotherapy protocol, risk category and prophylactic regimens.[6,19-22]

Diagnosis:

Invasive fungal infections are important causes of morbidity and mortality. Clarity and uniformity in defining these infections are important factors in improving the quality of clinical studies. A standard set of definitions strengthens the consistency and reproducibility of such studies. An international expert group consisting of U.S. mycoses study group (MSG) and the infectious disease group of the European

organization of research and treatment of Cancer (EORTC) has published an international consensus on diagnostic criteria of IFI in patients with cancer and hematopoietic stem cell transplantation (HSCT).[23,24] Which has been revised and now used the term invasive fungal disease (IFD) instead of invasive fungal infection.[24,25]

Three criteria are used to define invasive fungal disease:

Host factors, Clinical factors and microbiological factors which is supposed to assign a degree of certainty to the diagnosis. Three levels of probability are proposed; Proven, Probable and possible. To be defined as a proven infection fungal elements in tissue by histopathology or isolates from etiologic agents are required to be found in culture of sample from a normally sterile site such as blood, CSF and tissue in immunocompromised patients. Combination of a susceptible host, clinical signs compatible with fungal infections and mycological evidence or indirect (Non Culture/ Non Histopathology) evidence from nonsterile clinical sample like sputum and bronchoalveolar lavage were defined as probable IFIs. The category of possible IFD was defined more strictly to include only those cases with appropriate host factors and with sufficient clinical evidence consistent with IFD for which there was no mycological support.

Signs and symptoms:

Fungal infections might not have any specific manifestations. It might be accompanied by unexplained fever despite broad spectrum antibiotics or recurring febrile episodes after initial defervescence and or pulmonary infiltrates during antibiotic treatment. Bacterial and fungal blood stream infections can not be differentiated clinically. Pulmonary Aspergillosis may initially cause cough, pleural pain or hemoptysis. Sinusitis with local necrotic lesions during prolonged neutropenia is suggestive of mild infections. Fungal esophagitis may cause dysphagia and retrosternal burning. These symptoms also may be observed after h/o post cytarabine therapy or can be caused by Viral ulcers. Skin infiltrations during pancytopenia may be misinterpreted as thrombocytopenic purpura which could be due to yeast and mild infections or other pathogens. [26,27]

The clinical signs of hepatosplenic candidiasis can have persistent fever, hepatosplenomegaly, increased Alkaline phosphatase as well as fungal endophthalmitis (post uveitis) typically occur after neutrophils recovery. In systemic Candida infections other organs (Brain, Heart, Kidney, Bone) might also be affected by hematogenous spread. Most signs and symptoms are nonspecific. In patients with haematological malignancis IFI involving the central nervous system is caused generally by moulds.[28]

Investigations: The samples examined for microscopy should be done with gram stain and hematoxylin-eosin stain, special stain like for staining-demonstration of hyphe should be examined with PAS, Grocott's methaenamine Silver or calcofluor- white stain.[29] Culture**:** In general moulds are more difficult to isolate from clinical samples than Candida obtained from normally sterile body fluids (Blood, Pleural fluid and csf). [30,31] Assessment of sequential blood culture (two pairs from peripheral veins and central lines) is the method of choice to detect fungemia. CSF should be cultured with simultaneous antigen testing for C. neoformans.[32] The use of enriched media eg. Sabouraud's with 2 % glucose maybe helpful for isolation of fungus. All candidas should be isolated to the species level.[33] Any fungal culture from urine of a severely granulocytopenic patient without a urinary catheter may be interpreted as an indication of fungal infection.[34]

Antigen and antibody detection of blood and CSF: Various antibody and antigen test methods have been developed for the diagnosis of invasive candidiasis and Aspergillosis. Additionally antigen testing is an established diagnostic tool for Histoplasma capsulatum and C. neoformans. In immuno-compromised patients the detection of cryptococcal antigen in blood or/and CSF is highly indicative of cryptococcal meningitis.[35] Candida antigen testing is currently carried out using a latex agglutination test. An Elisa test for detection of Candida mannan antigen may be more sensitive. Antibodies against Aspergillous are frequently undetectable in immunocompromised patients.[36] Testing for Galactomannan (GM) antigen has yielded promising results in several clinical trials. A 90 to 100% specificity and 80 to 100 % sensitivity of the Galactomannan Elisa assay in granulocytopenic patients has been demonstrated.[37] Aspergillous GM may be detected in other fluids including Bronchoalveolar lavage and CSF where antigen detection seems to be superior to culture and to some PCR assay for identifying invasive infections.[38] Another method for serological diagnosis is Beta-D-glucans (BG). Detection of BG has the

potential to identify IFI caused by Candida species, Aspergillosis, Fusarium species, and Pneumocystis Jiroveci. [39-41]

So the recommendation of routine Candida antibody and antigen as well as Aspergillous antibody test is not recommended for haemato-oncological malignancy. Aspergillous antigen (GM) may actually be positive before clinical suspicion of an infection and may be useful for monitoring the response. Screening of BG in plasma for the diagnosis of IFI may be recommended in high risk hematology patients.

Imaging Procedures:

Early stages of pulmonary aspergillosis are often inconspicuous in conventional chest x Ray. HRCT or thin section CT detects typical infiltration pattern in an early stage.[42-44] These infiltrates consist of small nodules (1-3mm) surrounded by a halo are typically localized close to vessels. Perifocal haemorrhage should be considered suggestive of an invasive pulmonary Mycosis.[45-47] In this perspective several differential diagnosis is bleeding, embolism and Leukemic infiltration.[38,39] Early recognition of central hypodensity (Hypodensesign) of pulmonary infiltrates in CT series represents a valuable and highly fungal angiotropism with secondary hemorrhagic infarction.[40] So in patients with granulocytopenia, HRCT should be preferred to chest X-ray for primary diagnosis in high risk patients.

Liver-Spleen**:** Candidemia may lead to chronic disseminated candidiasis such as hepatosplenic candidiasis. A lesion with a hyperechoic centre and a hypoechoic rim (Bull's eye sign) size 5 to 20 mm may be detected by ultrasound.[48,49] Early diagnosis of a visceral organ infiltration can be made also by CT or MRI.[43,44] The role of FDG –PET ±CT scans has been found helpful in individual cases but can not discriminate between malignancy and infection.[50]

Gastrointestinal tract: Fungal infections in the gastrointestinal tract can be best visualized by CT and particularly by MRI scan.

CNS/Sinus/Eye: In patients with neurological symptoms such as seizures, change in mental status or persistent headache a cerebral CT scan is indicated for diagnosis of CNS IFI However MRI is preferred the regarding method of choice.[51] CT has been proven to be more reliable than MRI for exploring sinuses and superior in detecting bone destruction.[52-54] Plain radiography of the para nasal sinuses is of limited value. So recommendation for fungal infections in the CNS and paranasal sinuses can be best visualized by CT and MRI.[55,56]

Endoscopic methods**:** Endoscopic procedures particularly during granulocytopenia should be carefully weighted against odds.

Organ biopsy: If clinically feasible biopsy specimens should be taken from suspected area's.[57] Whenever possible an autopsy should be carried out in the deceased to collect important epidemiological information.

Polymerase chain reaction: Molecular diagnostic tools are promising and display high sensitivity and specificity.[58] Since fungal PCR is not a standardized or widely available diagnostic tool it is not included as a mandatory test in IFI diagnosis.

Antifungal Agents: Although there have been many newer antifungal agents, Invasive fungal infections continue to cause high morbidity and mortality in paediatric hematological malignancy patients.[12,20] So successful treatment of IFI is required to ensure the survival of this population . Currently there are four classes of drugs used in the treatment of IF I in children.[12] They are Azoles, Polyne, Pyrimidine analogues and Echinocondrins.[13] Appropriate use of Antifungal in the vulnerable populations is necessary for the treatment of IFI. Though safety and efficacy data; Toxicity etc including pharmacokinetics in children still needs trial based application.[22,59-61] Gulhan et al. in their study initiated antifungal agents in 149 neutropenic febrile episodes.[62] The most common antifungal agent used was Fluconazole. Fluconazole was mostly used for mucositis. Secondly used antifungal agent was L-AmB in 45 and Caspofungin in 15 episodes. Voriconazole was started in eight IFI episodes according to CT chest finding consistent with Aspergillosis.

Kaya et al. in their study showed that in 154 children with Acute Leukaemia 51.9 % received at least one course of antifungal treatment. L-AMB was successful in 15 out of 21 children as a single agent. All cases of Candidemia responded to L-AMB with a median period of 14 days with no recurrence.[63]

Kurosawa et al. in their study showing the use of antifungal agents in 35 IFI patients in 73 courses with hematological malignancies.[1] These were used as 1st line and salvage therapy. Voriconazol was the most

frequently used agent followed by Micafungin and L - AMB, Itraconazole and Fosfluconazole. Mostly the agents were used singly but combinations were also used. Voriconazole was used I/V or orally, Micafungin was administered I/V, Itraconazolewas used orally and Fosfluconazole was administered I/V. Successful outcome was there in 29.4 % (20/68) courses. A retrospective study in St. Jude by Abbasi et al. showed that 85% died within one year of the 66 patients.[61] There after no death occurred. Survival was similar for localized and disseminated disease categorized on the basis of clinical presentation. Of the disseminated Aspergillosis all except 2 were treated with AmphotercinB. Eight patients received 5-Flucytosine, 8 received Rifampicin, Six patients received both Rifampicin and Flucytosine, one received Ketoconazole and Itraconazole additionally with Amphotericin.

Byton et al in their study of invasive fungal infection began L-AMB empirically insuspicion in patients who had persistent fever for more than 5-7days and did not respond to antibacterial therapy.[8] Patients with invasive Aspergillosis who were refractory to primary treatment were put on Voriconazole therapy. Salvage therapy as combinations of Voriconazole and Caspofungin was used on those suggestive progressive signs and symptoms and persistent neutropenic fever.

Prophylaxis antifungal therapy: Few data are available on the epidemiology and clinical characteristics of IFI in children with Leukaemia. The incidence rate varies between 4.9 % and 29 % in leukemic children not receiving antifungal prophylaxis and between 2 and 4% among those given systemic antifungal prophylaxis during intensive chemotherapy.[16,64-72] Fluconazole prophylaxis has been shown to reduce the incidence and mortality in IFI in adult leukaemia patients undergoing chemotherapy. But a little is known about its use in childhood leukaemia especially in the developing world. Another study found overall incidence of IFI to be 13.6 % in children with Leukaemia who received Fluconazole prophylaxis, the incidence of proven IFI in this study was 7.2 %.[63]

Patients undergoing Allogenic Hematopoietic Stem Cell Transplantation (HSCT) are highly susceptible to IFI caused by Candida and Aspergillous. In one study Fluconazole decreases Candida IFI after HSCT and in one study there was improved survival,[65] which was a multicenter randomized double blind trial which compared Fluconazole versus Voriconazole for the prevention of IFI in patients with HSCT. This study demonstrated that in the context of intensive monitoring and structured empiric antifungal therapy 6 months event free survival and overall survival didn't differ in Allogenic HSCT recipients given prophylactic Fluconazole or Voriconazole.

Conclusion:

Invasive Fungal Infections (IFI) often appropriately called Invasive Fungal disease (IFD) causes significant morbidity and mortality in children with hematological malignancies. Predictors for IFI in children with Cancer include profound neutropenia, prolonged Corticosteroids use, Use of intensive chemotherapeutic regimens, and HSCT. Diagnosis of IFI should be based on EORTC/MSG criteria. There has been varied epidemiological statistics regarding incidence, causative organisms and response to antifungal agents. The commonest organisms so far identified in most of the series are Candida and Aspergillous species. The antifungal agents empirically used are Caspofungin, Liposomal Amphotericin-B, and Voriconazole. Prophylactic antifungal agents have shown some promises but the mortality is still very high. The ultimate strategy should be the prevention of fungal infections in this immunosuppressed group of children.

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