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Invasive Aspergillosis in Children: Where Do We Stand?

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Abstract

Invasive opportunistic fungal disease is a well-known complication in immuno deficient patients, adults as well as children. Apart from *candida*, *aspergillus* is by far the most common causative agent. Specific guidelines for the pediatric population concerning diagnosis, prophylaxis and treatment of invasive aspergillosis have been published recently and although this has been an important achievement, many challenges remain. This paper gives a short overview of the current guidelines, the recent advances in the diagnosis and management of invasive aspergillosis in the pediatric population. Besides we highlight the unmet needs of the pediatricians who are dealing with patients at risk of this complication.

Keywords: Invasive Aspergillosis; Children; Immunocompromised

Introduction

Invasive opportunistic Fungal disease (IFDs) is one of the most feared complications in patients primary or secondary immune deficiencies, resulting in high rates of morbidity and mortality. Depending on the circumstances, mortality is as high as 70% in some series [1]. Within this group, Aspergillus species are among the most common. Over the last decade, advances have been made concerning diagnosis, treatment and guidelines for adult patients have been developed and have been implemented in clinical practice. In pediatrics however, although advances have been made recently, data are more scarce. On the one hand, children are not small adults and data concerning diagnosis and treatment cannot be extrapolated without the necessary precaution. On the other hand, although IFDs is well known, it is much more rare in children than in adults [2], mostly because the underlying diseases such as cancer are much more rare in children. This makes it difficult to perform larger studies when evaluating the strengths of a diagnostic test or the efficiency of a new drug. Moreover, as prophylactic and empirical treatment is implemented in most treatment strategies, data concerning incidence and diagnosis will be hampered. This paper provides an overview of the diagnostic pitfalls, challenges in the treatment and follow up of these patients.

Epidemiology

Invasive fungal infections occur especially in children with a weakened immune system, either because of a congenital immunodeficiency such as severe congenital neutropenia, an infection such as HIV or because of immunosuppressive drugs like chemotherapy or corticosteroids. As the main risk factors are defined as a prolonged absolute neutrophil count below 500/mm^3, the use of corticosteroids and mucosal tissue damage [2,3]. This implicates that especially children treated for acute leukemia and those undergoing allogeneic stem cell transplantation have a markedly increased risk. The disease is much rarer in children with lymphoma's, solid tumors and after autologous stem cell transplantation [2].

Besides *Candida* species, *Aspergillus* is by far the most common cause of IFD. The respiratory tract including lungs and sinuses, is the most common primary site of interest. In approximately 30% of cases, the infection spreads to other organs, such as the brain and the skin [2,4]. Exact data concerning the incidence of invasive aspergillosis (IA) are difficult to obtain. First, there are many factors related to the environment. For example, construction site in the neighborhood of the ward leads usually leads to an increase in infections [5]. Secondly, the use of prophylaxis and the incidence of resistance vary from center to center [6]. Another obstacle is that in children, clinicians might be reluctant to perform more invasive diagnostic tests such as bronchoalveolar lavage or a biopsy, leading to a lack of information concerning the exact pathogen involved (Figures 1 and 2). Still, data indicate that *Aspergillus Fumigatus* is the most frequent cause of IA and that other species such as *A. Flavus* are much more rare [2].

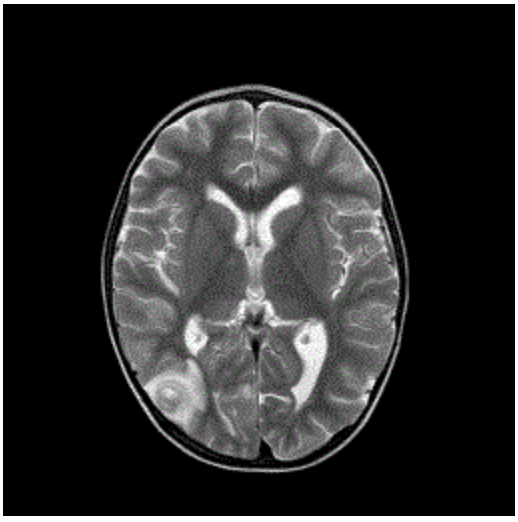

Figure 1: Typical image of invasive aspergillosis in the lung with an air crescent sign in a 15 years old girl

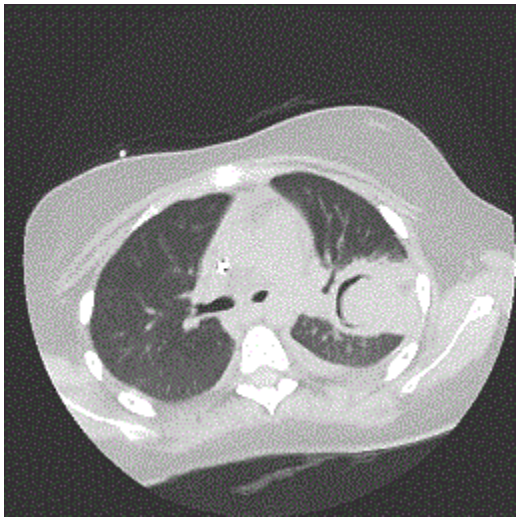

Figure 2: Primairy invasive aspergillosis of the brain. This patient presented with convulsions and no fever

Clinical Presentation

The clinical presentation is variable, thus making the diagnosis difficult. Historically, IA should be suspected in immunocompromised children with fever for more than 96 hours. However, the absence of fever does not exclude this diagnosis. Besides, symptoms vary according to the involved organs and can lead to cough, pleural pain, hemopteu, headache or convulsions. This makes it difficult for clinicians to follow strict guidelines and underlines the importance that they are aware of the possibility of such infections, especially in high risk patients. In general, clinicians treating heavily immunocompromised patients with fever, cough, convulsions, skin lesions should be aware of the possibility of an invasive fungal infection as soon as the symptoms start and try to exclude or prove this diagnosis without too much delay.

Diagnosis

Based on host factors, clinical criteria and obtained test results, IFDs can be classified as proven, probable and possible [7]. In order to have a proven infection, cultures or histological evidence has to be obtained from a site that is normally sterile, indicating that a biopsy needs to be performed and that broncho alveolar lavage isn't enough. This is not often feasible, especially in children. Therefore, clinicians too often have to rely on indirect testing such as imaging studies and the detection of anti aspergillus antigens in the peripheral blood or broncho alveolar fluid.

Imaging studies are fast and easy to access. Usually, CT scan remains the study of choice as standard radiography is usually not sensitive enough, especially in immunocompromised children lacking neutrophils. In adult patients, there are specific findings such as the halo sign, pulmonary nodules, and the air crescent sign and, in severe cases, cavitation [8]. However, these findings are much less obvious in children [4,8,9]. A single center review study conducted by Thomas et al showed that children had less specific findings such as segmental and multilobar consolidation, perihilar infiltrates, multiple small nodules, peripheral nodular masses and pleural effusions. Small cavitating nodules were present on CT in two of eight children [9,10]. Therefore, in high risk patients with radiological abnormalities treatment should be initiated as soon as possible, preferably after a tissue specimen has been obtained [2].

The galactomannan assay is a serological marker that is widely used to screen for invasive as mold infection [8]. This ELISA test detects the galactomannan antigen, which is a part of the cell-wall of all aspergillus species. The test can be applied on serum, but also broncho alveolar or cerebrospinal fluid. These last two tests should be performed in case of a suspicion of an invasive fungal disease. The test on serum is easy to use and should be implemented as a screening test that is performed on serum twice weekly. Although there have been some concerns about the sensitivity in children, recent data show that there is no difference between adults and children and children and that the sensitivity in children is 0.76 (95%CI 0.62- 0.87) [2]. Although there has been some variation in literature concerning the cut off value, the recent ECIL -4 guidelines published by Groll et al. indicate that a cut off value of >0.5 is optimal [2]. However, it should be taken into account that false positivity can be caused by several factors, such as the administration of betalactmases and blood products, bacterial or Candida sepsis, bowel inflammation such as seen during gastroenteritis, mucositis or graft versus host disease of the bowel, and a false negative test might be seen when antifungal prophylaxis is given [11].

More recently, the Beta 1,3-d-glucan assay has been proposed as a new screenings test for IA [10]. This test, which is not selective for aspergillosis and can also be used to screen for a wide spectrum of other infections [12]. Unfortunately, data on the use of this test in the pediatric population are lacking and it is therefore not recommended as a test for IA in children [2].

Another approach is to screen for anti aspergillus antibodies [13]. This test, which has been used for over 50 years, has several disadvantages. First of all, the antibodies only appear after a certain amount of time which is too late to use it as a diagnostic test. Besides, false negative results can be obtained in immunocompromised children who might be lymphopenic as well as neutropenic and therefor might not be able to mount a good antibody response. It can therefore only be used in patients with an intact immune system but also at risk of IA, such as cystic fibrosis patients. There might however be a certain value of this test in this last group of patients in monitoring the evolution of the disease after implementation of treatment.

All these tests are valuable to screen for IA, but in case of a real suspicion more invasive procedures such as bronchoalveolar lavage or biopsy should be performed because it will allow identification of the type of IFDs as well as giving the opportunity to test for drug resistance, thus protecting the patient form receiving inadequate or suboptimal treatment.

Treatment and Prophylaxis

When dealing with IFD several strategies are applied: prophylaxis, empyrical treatment and treatment of a probable or proven fungal infection. Whether or not prophylaxis is used in a certain center depends on many factors such as local epidemiology, the possibility for isolation in hepa filtered rooms and reimbursement strategies in a certain country. However, it is generally recommended to administer prophylaxis in high risk patients [2,14]. Empyrical treatment is widely

accepted as the treatment of choice in neutropenic children with persisting fever after initiation of broad spectrum antibiotics. Of course it is recommended in these patients to perform the necessary diagnostic procedures leading to treatment of a possible or probable disease, as this will influence the duration and type of the treatment.

Amphotericin B is the oldest antifungal and until recently, the only possibility to treat IA. Usually, this drug is administered in a lipid associated formulation intravenously. It is approved for empyrical therapy as well as treatment of proven or probable fungal infection. Over all, pediatric patients support the drug rather well [15]. In the prophylactic setting, there has been some research regarding the optimal dosage of the drug. Regimens using twice weekly administrations or low daily doses as well as inhaled administration have been explored in adults [16].

Fluconazole is one of the most commonly used drugs but has an activity limited to Candida species and therefore not recommended as prophylaxis for IA. Itraconazole has shown to be efficient in treatment of IFD [15] but isn't commonly used anymore since the introduction of other, more effective antifungal drugs. However, in the prophylactic setting it still has a place [15].

Another azole derivate is Voriconazole. This drug has been proven to be useful in treatment and prevention of IA in adults as well as children [17,18]. The main issue is that, in the pediatric population, the metabolism is much faster as compared to adults, leading to decreased plasma levels thus requiring higher doses [19]. Because of this, drug monitoring is recommended, although data concerning optimal dosing in children are still insufficient. The last azole derivate is Posaconazole. This oral, second generation azole derivate is not approved for patients less than 18 years of age, but data show that the drug is well tolerated and effective against Aspergillus species, as well as against other fungi such as Mucormycosis [20]. Although data are limited, the drug appears to be safe in a prophylactic and treatment setting [21,22]. Of the azole derivates, only Itraconazole and Fluconazole are approved for prophylactic use in the pediatric setting, whereas Voriconazol is only approved for proven or probable aspergillosis.

A different group of drugs are the echinocandins, containing Caspofungin, Micafungin and Anidulafungin. Caspofungin and Micafungin are approved for pediatric patients, whereas concerning anidulafungin, there are very little data. Caspofungin, that can only be administered by intravenous route, has been shown to be effective as prophylaxis as well as in the empirical as the therapeutical setting [23-26]. The drug is approved for children and infants for empirical therapy for neutropenic patients with persistent fever as well as second line antifungal therapy in patients with a proven IA. It has proven to be effective in at least a large part of patients with IA who showed resistance to other drugs [27,28] Therefore, it provides a valuable alternative for patients with resistant or recurrent disease as well as in the empiric setting.

Although the possibilities for treatment of IA have improved markedly over the last decade, and guidelines concerning prophylaxis and treatment have become available for the pediatric population, there are still several questions to be answered. One of the most important issues is the question how long a treatment should be continued after resolution of the infection, as the relapse rate varies between 30 and 50% in adults [2]. Very little data are available for neither the adult nor the pediatric population, but it is recommended to continue treatment till the recovery of neutropenia [2]. Off course, for patients treated for acute leukemia, who will have repetitive episodes of neutropenia it might even be necessary to continue till the start of the less intensive maintenance therapy because relapses can occur easily. Criteria how to monitor for a pending relapse are scarce, especially in children.

Conclusion

It is recognized now that IA in children needs another approach than in adults. An important step forward has been made by the development of specific guidelines for the pediatric population concerning diagnosis and treatment. However, improvement is still warranted in many aspects. The diagnoses remains difficult in many cases as the Galactomannan test cannot always be relied on and imaging studies are sometimes less clear as compared to adults. Especially in the prophylactic setting, but also in the therapeutic area, pediatric oncologist do not always have access to the same drugs as adults. Another issue is the development of resistance of some species to certain drugs, which can be an important problem in certain areas. Finally, concerning the duration of treatment and the follow up to screen for relapses criteria have not been developed yet.

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