Invasive Candida Infections (ICI) in Pediatric Population of a Tertiary Care Hospital in United Arab Emirates (UAE): Management and Time to Negative Culture

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Accepted 2017-08-20; Published 2017-09-06

Abstract:

Background: Invasive candida infections (ICI) are a growing problem in critically ill patients. Candida species are the most common agent responsible for invasive fungal infections in children. Timely diagnosis and proper selection of antifungal therapy are of paramount importance for a favorable outcome. The increasing rate of non-albicans candida is becoming a real challenge when choosing an empirical antifungal therapy since a large percentage of them are resistant to azoles. This study aims at identifying the most commonly used antifungal agents in our institute and their success measured by the time needed to reach a negative culture (TNC) in cases of candidemia and candiduria.

Methods:

We performed a retrospective cohort study of all children (15 years and younger) with invasive candida infections, admitted to Tawam Hospital from the 1st of January of 2008 to the 31st of December 2015.

Results:

Fluconazole seems to be the most common choice of our pediatricians in treating urine ICI (65%) while Amphotericin B Lipid complex is the most common choice in treating blood ICI (56%). Amphotericin B Lipid Complex was associated with the shortest TNC both in treating urine ICI and blood ICI.

Conclusions:

Unfortunately, there aren’t many prospective studies in the literature comparing the efficacy of the major antifungal agents in treating pediatrics ICI. Therefore, we hope that this study, despite being retrospective, will shed some light on the utilization of Amphotericin B Lipid Complex in treating pediatrics ICI.

Keywords:

Invasive candida infections, Antifungals, Time to negative culture

Abbreviations:

ICI: Invasive Candida Infections
TNC: Time to negative culture
Introduction:
Invasive Candida infections (ICI) are a growing problem in critically ill patients. Candida species (Candida albicans, Candida glabrata, Candida tropicalis, Candida parapsilosis, and Candida krusei) are the most common agents responsible for invasive fungal infections in children. Unlike oral candidiasis and vaginal candidiasis, ICI are serious infections that can affect different parts of the body including: the blood stream, heart, kidneys, brain, eyes and bones. ICI refers to systemic infection with Candida of either vital organs or normally sterile body fluid (blood, cerebrospinal fluid [CSF], or urine acquired by sterile catheterization or suprapubic aspiration). ICI are associated with high mortality and morbidity rate as well as high health care costs. In addition, ICI are associated with poor neurodevelopmental outcomes among survivors. Over the past two decades, a significant increase in the incidence of ICI has been observed. Candida species now represents the third most common agent associated with healthcare-associated bloodstream infections in children. Despite the emergence of Candida non albicans in pediatric population, Candida albicans remains the main Candida species associated with ICI in children. Timely diagnosis and proper selection of antifungal therapy are of paramount importance for a favorable outcome. The selection of systemic antifungal in patients with ICI depends on the identification of Candida species involved, many of which are known to be resistant to azole antifungal.

In this retrospective study we reviewed the antifungal agents which were used in treating patients admitted with ICI to Tawam Hospital from the 1st of January of 2008 to the 31st of December 2015. Our study population included all children 15 years old and younger with culture proven Candida infection. Tawam hospital is a major tertiary care hospital in United Arab Emirates with a total of 150 dedicated acute pediatric beds divided between general and subspecialty pediatrics, pediatric surgery, Neonatal Intensive Care, Pediatric Intensive care and Hematology/Oncology wards.

Methods:
Our study is a retrospective cohort study. The medical records for all pediatric patients (15 years and younger) who were admitted with positive urine and blood cultures for candida in Tawam hospital during the study period were reviewed. We identified the choice of antifungals used in each case in addition to the TNC. A total of 149 patients were included in this study. 54 patients satisfied the inclusion criteria (i.e: had complete medical records and received a single agent throughout their therapy). Only those 54 cases are included in this study.

Results:

Figure 1:

<table>
<thead>
<tr>
<th>Antifungals used in urine ICI</th>
<th>Antifungals used in blood ICI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal Amphotericin B</td>
<td>Caspofungin</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>Liposomal Amphotericin B</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Amphotericin B lipid complex</td>
</tr>
</tbody>
</table>

International Journal of Contemporary Research and Review, Vol. 8, Issue. 9, Page no:MS 20283-20286
Fluconazole was the most commonly used antifungal (13 out of 20 cases) in treating urine ICI with an average TNC of 8.5 days, while Liposomal Amphotericin B (which was used in 5 out of 20 cases) had an average TNC of 7.6 days and Amphotericin B Lipid complex (which was used in 2 out of 20 cases) had an average TNC of 3 days (Figure 1).

Amphotericin B Lipid complex was the most commonly used antifungal (19 out of 34 cases) in treating blood ICI with an average TNC of 4.4 days, while Liposomal Amphotericin B (which was used in 12 out of 34 cases) had an average TNC of 10 days and Caspofungin (which was used in 3 out of 34 cases) had an average TNC of 7.8 days (Figure 2).

Figure 2:

Discussion:

Since 2008, Fluconazole seemed to be the preferred choice of our pediatricians in treating urine ICI while Amphotericin B Lipid complex was the most common choice in treating blood ICI. It seems that Amphotericin B Lipid complex was associated with the shortest TNC in treating both urine and blood ICI.

Amphotericin B is one of the oldest antifungals and is known to have the widest spectrum against the different fungi. However, the use of Amphotericin B has been limited historically due to the common side effects mainly the renal ones. In order to minimize those side effects, different lipid formulations of Amphotericin B have recently been manufactured including a Lipid Complex formulation and a Liposomal formulation. These two formulations are different in their lipid composition, shape, size, stability, pharmacokinetics and toxicity (6)(Table 1).

A review article by Martino et al compared all publications between 1997 and 2003 in relation to the Amphotericin B Lipid formulations. They concluded that Amphotericin B Lipid Complex was safe and effective when used in pediatrics and adult patients with refractory ICI (7). In our study, Amphotericin B Lipid Complex had a bit of an advantage in being faster in clearing both urine and blood ICI. Similar findings were published by Fleming et al in 2001 who compared the outcomes of oncology patients who received one of the two formulations for treating ICI (8). Another study by Cannon et al also reached similar conclusions (9).

With that being said, we would like to emphasize that our results are majorly limited by the retrospective nature of the study and the limited number of patients. Due to the scarcity of ICI, most published studies suffered from the same limitations. We believe that there is still a need for properly randomized prospective studies in pediatrics to compare the available antifungal agents in the management of ICI.
Table 1:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Liposome amphotericin B</th>
<th>Amphotericin B lipid complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Spherical liposomes</td>
<td>Ribbon-like complexes</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Cl = 11 mg/L/h/kg</td>
<td>Cl = 436 mg/L/h/kg</td>
</tr>
<tr>
<td>Toxicity</td>
<td>20 mg/kg = minimal nephrotoxicity</td>
<td>10 mg/kg = mild nephrotoxicity</td>
</tr>
<tr>
<td>Mode of action</td>
<td>Liposome targeting to fungal cell wall with release of amphotericin B into fungus</td>
<td>Release of amphotericin B from complexes, possibly host macrophage- and phospholipase-mediated</td>
</tr>
<tr>
<td>Effect of drug concentration and localisation on therapeutic efficacy</td>
<td>Comparable efficacy to amphotericin B lipid complex even with lower liposome amphotericin B tissue concentrations</td>
<td>Higher concentrations in lung, liver and spleen as compared to liposome amphotericin B Uptake by macrophages</td>
</tr>
<tr>
<td>Effect of drug concentration and localisation on therapeutic efficacy</td>
<td>Targeting of liposomes to fungal infection sites in tissues as well as uptake by macrophages</td>
<td></td>
</tr>
<tr>
<td>Toxicity and efficacy in Lung infections</td>
<td>Efficacy without nephrotoxicity at 5–20 mg/kg</td>
<td>Efficacy without nephrotoxicity at 5 mg/kg; nephrotoxicity and decreased efficacy at 15 mg/kg</td>
</tr>
<tr>
<td>High-dose treatments</td>
<td>Highest tolerated doses in infected animals = 30–50 mg/kg</td>
<td>Highest tolerated doses in infected animals = 12–15 mg/kg</td>
</tr>
</tbody>
</table>

References:

8. Fleming et al. Comparison of Amphotericin B Lipid Complex (ABLC) vs. AmBisome in the Treatment of Suspected or Documented Fungal Infections in Patients with Leukemia, 2001(31)
9. Cannon et al. A Prospective and Retrospective Analysis of the Nephrotoxicity and Efficacy of Lipid-Based Amphotericin B Formulations. Pharmacology publications, 2001(21) 1107-1114

Tables: