Renal Impairment Related to Different Antifungal Medications in Cases of Invasive Candida Infections in Tawam Hospital Pediatric Population between 2008-2015

Noura Jasim¹, Mouza Al Ameri ¹, Hind Al Dhaheri ¹, Muneera Al Mansoori ¹, Fatima Al Yahyaei ¹, Eiman Al Kaabi ¹, Fatima Al Ahbabi ¹, Salwa Al Kaabi ², Hossam Al Tatari ³

Pediatric Residency, Academic Affairs, Tawam Hospital, Al Ain, UAE.
Division of General Pediatrics, Pediatric Department, Tawam Hospital, Al Ain, UAE.
Division of Pediatric Infectious Diseases, Pediatric Department, Tawam Hospital, Al Ain, UAE.

Abstract:

Background: As a tertiary hospital, Tawam Hospital has been dealing with more and more complex pediatric cases. Such cases are often at higher risk of developing Invasive Candida Infections (ICI). Amphotericin B preparations continued to provide the widest coverage for all Candida strains and have been the drug of choice for definitive and empirical therapy in our institute. However, renal complications have always been a concern with this group of antifungals. Numerous studies have reported contradicting results in terms of which Amphotericin B preparation has less renal side effects. Therefore, we are here to report our own experience.

Methods: We performed a retrospective cohort study of all children (15 years and younger) with ICI who were treated at Tawam Hospital from 2008 to 2015.

Results: Out of the 40 patients included in this study, 7 patients were treated with Amphotericin B Liposomal (ABL). Two of them had elevated Urea/Creatinine after initiating the therapy. 11 patients were treated with Amphotericin B Lipid Complex (ABLC). Two of them had elevated Urea/Creatinine after initiating the therapy. Fluconazole was used in 14 patients. 2 of them had high Urea/Creatinin before therapy which did not show any further deterioration while on therapy. Two patients were treated with a combination of Fluconazole and LAB. They both had high Urea/Creatinine before and after therapy. However, one of them was known to have renal failure. While 4 cases were treated with the combination of Fluconazole and ABLC among whom one patient had high Urea/Creatinine before therapy that went down while on therapy.

Conclusions: Although Amphotericin B is known to be associated with renal side effects, the newer preparations seem to offer a much safer alternative. Among the two available preparations, ABLC seemed to be safer in our experience. Fluconazole continued to have minimal renal side effects. However, just like most of the published studies on this topic, our study was limited by the small number of patients included and the retrospective nature of the study.

Keywords: Invasive candida infections, Renal impairment, Amphotericin B Lipid Complex, Amphotericin B Liposomal, Fluconazole.

Abbreviations:

ICI: Invasive Candida Infections, Amphotericin B Lipid Complex (ABLC), Amphotericin B Liposomal (ABL), CSF: cerebrospinal fluid, CLEAR: Collaborative Exchange of Antifungal Research,
Introduction:

Invasive Candida Infections (ICI) in children appear to have increased over the past few decades (1). Candida albicans is the most frequently isolated species overall in children and adults, but the rates vary depending on the location and the patient population studied (2). However, the rate of Candida non-albicans species invasive infections seem to be rising worldwide, and even exceeding Candida Albicans in some countries as a cause of ICI (3).

Most available antifungal agents have reasonably broad activity against Candida albicans and the more commonly isolated non-albicans species. The selection of systemic antifungals in patients with ICI depends on the identification of Candida species involved, some of which are known to be often resistant to azole antifungals such as Candida Krusii and Candida Gelbrata (4).

In this retrospective study wereviewed the renaleffect of antifungal therapy among pediatric patients treated for ICI with different antifungals in Tawam Hospital between 2008-2015.

Our study population included all children from 0-15 years with culture proven Candida infections from blood, urine or CSF. 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:

We retrospectively studied all positive candida cultures from blood, urine and CSF from children age 0-15 between 2008-2015. The total number positive cultures were 149 some of which were repeated cultures from the same patients. 59 patients in total have received antifungals. However, only 40 out of 59 had their urea and electrolyte checked before and after starting medications. Only those patients were included in our study.

Results:

We divided the patients according to their age group as follows: Newborns (0-1months), Infants (1month-1year), Children (above 1 year), and our reference value for urea and creatinine were as below (Table 1):

<table>
<thead>
<tr>
<th>Age</th>
<th>Urea</th>
<th>creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-19mg/dl</td>
<td>0.3-1mg/dl</td>
</tr>
<tr>
<td></td>
<td>0.7-6.7 mmol/L</td>
<td>27-88 micromol/L</td>
</tr>
<tr>
<td>Newborns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>5-18mg/dl</td>
<td>0.2-0.4mg/dl</td>
</tr>
<tr>
<td></td>
<td>1.8-6.4 mmol/L</td>
<td>18-35 micromol/L</td>
</tr>
<tr>
<td>children</td>
<td>3-25mg/dl</td>
<td>0.3-0.7mg/dl</td>
</tr>
<tr>
<td></td>
<td>1.1-8.9 mmol/</td>
<td>27-62 micromol/L</td>
</tr>
</tbody>
</table>

In our study, out of the 40 patients included, 7 patients were treated with ABL. Two of them had elevated Urea/Creatinine after initiating the therapy. 11 patients were treated with ABLC. Two of them had elevated Urea/Creatinine after initiating the therapy (Figure 1). Fluconazole was used in 14 patients. 2 of them had high Urea/Creatinin before therapy which did not show any further deterioration while on therapy. Two patients were treated with a combination of Fluconazole and ABL. They both had high Urea/Creatinine before and after therapy. However, one of them was a known to have renal failure. While 4 cases were treated with the combination of Fluconazole and ABLC among whom one patient had high Urea/Creatinin before therapy that went down while on therapy.
Discussion:

It is critical to start empirical antifungal therapy whenever ICI is suspected. However, choosing the appropriate empirical antifungal agent is very challenging mainly that it is very hard to grow the offending agent in a large percentage of patients. Therefore, it is paramount that the treating physician be aware of the local epidemiology data as well as the basic pharmacology of the available antifungal agents. There have been some new antifungal agents in the last decade; however, many of them have not been well studied among children and infants. Hence, clinicians often feel obliged to use old agents with wide coverage for yeast and molds such as the Amphotericin B preparations (5).

In our study we focused on the renal effect of the two main Amphotericin B preparations. Although they both seemed to increase the BUN/CRE in a small percentage of patients, this seemed to occur less often with ABLC in comparison with ABL (2/11 Vs 2/7)

Up on review of the literature, we identified at least ten different similar studies as shown in figure 2.

Pappas et al (6) focused on a large group of patients who were treated with ABLC and demonstrated a very low rate of renal complications.

However, the other studies –which provided comparison between the two agents- revealed contradicting results. While McKechnie M et al (7), Couch K et al (8), Slain et al (9), Fleming et al (10) and Wingard et al (11) concluded that ABLC had higher renal side effects, interestingly enough, other researchers such as Lopez Sastre et al (12), McTaggart et al (13), Cannon et al (14) and fortune et al (15) reported the opposite.
Out of those studies, the Pappas et al. study seemed to include the largest number of patients. Pappas et al. reviewed all registered patients in the CLEAR (the Collaborative Exchange of Antifungal Research) multicenter database. The authors retrospectively investigated the renal safety of ABLC treatment in this large population of patients with fungal infections. The CLEAR database included records of 3514 patients, which were classified to those older and younger than 18 years of age. The authors concluded that, the two age groups showed similar incidence of doubling of S-Cr level from baseline and new need for dialysis as shown in table 2.

It was noticed that renal function impairment was reversible after cessation of treatment with Amphotericin B and even with continuation of therapy in certain occasions. This could possibly be the result of tissue remodeling and repair mechanisms (16, 17).

**Table 2:**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Baseline S-Cr level, median (range), mg/dL</th>
<th>Change in C&lt;sub&gt;C1&lt;/sub&gt;, Median (range), mL/min</th>
<th>P</th>
<th>No. (%) of patients</th>
<th>P</th>
<th>Increase in S-Cr level to &gt;2.5 mg/dL, No. (%) of patients</th>
<th>P</th>
<th>New dialysis, No. (%) of patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (N = 3514)</td>
<td>1.4 (0.08–6)</td>
<td>-3 (−119 to 118)</td>
<td>...</td>
<td>468 (13)</td>
<td>...</td>
<td>412 (12)</td>
<td>...</td>
<td>92 (3)</td>
<td>...</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 years (n = 454)</td>
<td>0.7 (0.1–6)</td>
<td>0 (−106 to 106)</td>
<td>...</td>
<td>71 (16)</td>
<td>...</td>
<td>27 (6)</td>
<td>...</td>
<td>12 (3)</td>
<td>...</td>
</tr>
<tr>
<td>≥18 years (n = 3048)</td>
<td>1.6 (0.08–6)</td>
<td>-3 (−119 to 118)</td>
<td>.008</td>
<td>396 (13)</td>
<td>.110</td>
<td>386 (13)</td>
<td>&lt;0.001</td>
<td>80 (3)</td>
<td>.975</td>
</tr>
<tr>
<td>Status prior to start of ABLC therapy&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractory&lt;sup&gt;b&lt;/sup&gt; (n = 1411)</td>
<td>1.2 (0.08–6)</td>
<td>-5 (−111 to 99)</td>
<td>.033</td>
<td>220 (18)</td>
<td>.282</td>
<td>151 (11)</td>
<td>.397</td>
<td>25 (2)</td>
<td>.209</td>
</tr>
<tr>
<td>Underlying renal disease, prior antifungal therapy (n = 64)</td>
<td>2 (0.3–6)</td>
<td>0.5 (−107 to 52)</td>
<td>&lt;0.001</td>
<td>11 (13)</td>
<td>.307</td>
<td>14 (17)</td>
<td>.056</td>
<td>4 (5)</td>
<td>.027</td>
</tr>
<tr>
<td>Underlying renal disease, no prior antifungal therapy (n = 945)</td>
<td>2 (0.15–6)</td>
<td>0 (−99 to 118)</td>
<td>&lt;0.001</td>
<td>83 (9)</td>
<td>&lt;0.001</td>
<td>133 (14)</td>
<td>.025</td>
<td>44 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intolerance&lt;sup&gt;c&lt;/sup&gt; (n = 573)</td>
<td>1.4 (0.2–6)</td>
<td>0 (−108 to 101)</td>
<td>&lt;0.001</td>
<td>60 (11)</td>
<td>&lt;0.001</td>
<td>54 (9)</td>
<td>.855</td>
<td>14 (2)</td>
<td>.072</td>
</tr>
<tr>
<td>No prior antifungal therapy/no renal disease (n = 431)</td>
<td>1 (0.1–6)</td>
<td>-10 (−117 to 101)</td>
<td>...</td>
<td>77 (18)</td>
<td>...</td>
<td>42 (10)</td>
<td>...</td>
<td>4 (1)</td>
<td>...</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior AmB (n = 2056)</td>
<td>1.3 (0.08–6)</td>
<td>-5 (−119 to 118)</td>
<td>&lt;0.001</td>
<td>311 (15)</td>
<td>&lt;0.001</td>
<td>230 (11)</td>
<td>.290</td>
<td>50 (2)</td>
<td>.408</td>
</tr>
<tr>
<td>Prior AmB (n = 1398)</td>
<td>1.6 (0.19–6)</td>
<td>0 (−117 to 101)</td>
<td>...</td>
<td>146 (10)</td>
<td>...</td>
<td>173 (12)</td>
<td>...</td>
<td>40 (3)</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** Statistical analysis was performed by using the median scores test for continuous variables and χ<sup>2</sup> or Fisher’s exact test, as appropriate, for categorical variables. AmB, amphotericin B deoxycylolate; C<sub>C1</sub>, predicted creatinine clearance; S-Cr, serum creatinine.

<sup>a</sup> Values in this subsection compare each category with patients in the “no prior antifungal medication/no underlying renal disease” category.

<sup>b</sup> Twenty-two percent of these patients also had underlying renal disease.

<sup>c</sup> Intolerance included infusion-related toxicity, increasing S-Cr level, or hepatotoxicity.
Conclusions:

Although Amphotericin B is known to be associated with renal side effects, the newer preparations seem to offer a much safer alternative. Among the two available preparations, Amphotericin B Lipid Complex (ABLC) seemed to be safer in our experience. Our results match the results of several other studies. Fluconazole continued to have minimal renal side effects. However, our study is limited by the small number of patients included and the retrospective nature of the study. With that being said, this seems to be the case with most studies of invasive candida infections available in the literature.

References:


International Journal of Contemporary Research and Review, Vol. 8, Issue. 11, Page no: MS 20384-20389
doi: http://dx.doi.org/10.15520/ijcrr/2017/8/11/373
Noura Jasim et al. Renal Impairment Related to Different Antifungal Medications in Cases of Invasive Candida Infections in Tawam Hospital Pediatric Population between 2008-2015

16. Gallis Ha, Drew RH, Pickard WW. Amphotericin B: 30 years of clinical experience, 12 (1990), pp. 308-29

Tables:
Table 1 Retrieved from: The Harriet Lane Handbook, A manual for pediatric House officers, nineteenth edition, P: 642 and 647