THE USE OF FLUCONAZOLE IN NOSOCOMIAL CANDIDIASIS IN PEDIATRICS

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ABSTRACT

Due to the high rate of Amphotericin B related toxicity, fluconazole at 5 mg/kg was used as the first line antifungal in 33 patients with nosocomial Candida infection, from January – July 1996. The dose of fluconazole was 5mg/kg/day. Subjects were 65% were male, 34% were female. 34% were less than one month old, of which 50% were born preterm. 21% were between 1 month and 6 months, 6% from 6 mos.-1yr, 12.5% 2-3 yrs., 15.6% 4-9 yrs. and 9.3% 14-15 yrs. Two patients had leukemia as their underlying illness. All patients had received an average of 4 broadspectrum antimicrobials for more than 1 week at the time Candida was isolated. 75% of the cases were intubated and 97% were being treated as sepsis with nosocomial pneumonia. The intravenous route was preferred when Candida was isolated from the blood or from more than 2 sites or from the urine if the patient was unstable and was thought to represent hematogenous dissemination. The average duration of therapy was 13 days if isolated from more than one site, 10 days, if isolated from urine and 13.5 days if isolated from the blood provided repeat cultures were negative. Dose adjustment was done in two patients who had cholestatic jaundice secondary to total parenteral solutions and sepsis and both were eventually had to be shifted to Amphotericin B due to clinical deterioration. No patient required discontinuation due to adverse effects. Treatment failure was noted in only 5/33 cases (9%). This was based on clinical deterioration and persistently positive fungal cultures despite a 5 day therapy with Fluconazole. Fungal isolates of Candida krusei (2/5), Candida non-albicans (2/5), and Candida sp (1/5) were associated with failure. In all 5 cases Fluconazole was shifted to Amphotericin B. There were 3 mortalities observed 2 of which were Candida related. It is concluded that Fluconazole can be used safely and effectively as a first line therapy for nosocomial invasive Candida Infection in pediatric patients.

Key words: *Fluconazole*
Nosocomial
Candidiasis

INTRODUCTION

Antemortem diagnosis of invasive Candida infection is difficult and the clinical relevance of fungemia can often be underestimated particularly if only 1 blood culture is positive for the fungus. Studies have shown that concomitant bacteremia can decrease the yield of fungal cultures. (1) Fraser, et. al. points out, that, there is much difficulty in stratifying patients who are likely to develop Candida infection. (2) In very ill patients with several underlying disease conditions or with risk factors such as intensive chemotherapy, organ transplants, extensive burns, surgery, broad spectrum antibiotics, steroid therapy, long term indwelling catheters and HIV, (1), total parenteral nutrition, there exists a high probability for developing candida superinfection. A review of the nosocomial infections at the UP-PGH Department of Pediatrics from Jan. 1994 – July 1996, shows a steady increase in the rate of Candida infection, (table 1), furthermore, from May 1996 – July 1996 Candida has been the number 1 nosocomial isolate. We can only speculate that this may have been secondary to aggressive use of multiple broad spectrum antibiotics. With the rising threat of Candida superinfection, there is a need for an antifungal which is less toxic yet as effective as Amphotericin B, in the treatment of patients whose Candida isolates were presumed to be actual infections or who are empirically treated as cases of invasive candidiasis on clinical grounds while awaiting culture results.

Table 1 Summary of the Top 5 Nosocomial Isolates at the UP-PGH Department of Pediatrics from January 1994 - July 1996

RANK	1994	1995	1996 (FEB. - JUL.)
1	Enterobacter 21.4%	Klebsiella 27.4%	Candida 15.8%
2	Acinetobacter 18.2%	Candida 20.14%	Enterobacter 10.06%
3	Pseudomonas 17.3%	Enterobacter 17.3%	Pseudomonas 9.75% Klebsiella 9.7%
4	Candida 17.2%	Pseudomonas 14.9%	Acinetobacter 5.18%
5	Klebsiella 15.2%	Acinetobacter 5.96%	E. coli 1.83%

In the therapy of Candida infection, Amphotericin B, alone or in combination with flucytosine had remained as the mainstay of systemic fungal infection therapy, (4). However, its use has been complicated by its toxicity (5,6), which include renal and bone marrow toxicity; it has poor CSF

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penetration and has to be administered via intravenous route. (3) Various problems have also been associated with flucytosine, which is characterized by a narrow spectrum of activity and potential for bone marrow toxicity and frequent development of resistance. (6)

The recent development of the second generation azole Fluconazole, has marked another milestone in antimycotic therapy. (4) Fluconazole is a triazole antifungal drug which has a pharmacokinetic profile characterized by its high water solubility, low affinity for plasma proteins, and metabolic stability. (5) These combination of attributes recommends its use for the treatment of both superficial and systemic infections. Its successful use among infants and children have likewise been documented. (3,8,9,10).

OBJECTIVES

This study reviews the use of fluconazole among pediatric patients, referred to the Pediatric Infectious Disease Section with culture proven Candida infection in PGH from Jan. 1996 to July 1996. Specifically this study describes the following:

a. demographic profile of the study population as to age and sex

b. clinical profile of the study population as to: type of candida infection and species of candida isolated

c. dose/duration/route of Fluconazole

e. outcome of therapy on clinical and bacteriologic criteria

Response to therapy was evaluated based on the following:

I. ***Clinical response***
   a. *cure* – disappearance of all pretreatment signs and symptoms

   b. *improvement* – satisfactory remission but without complete disappearance of signs and symptoms

   c. *failure* – no signs of remission of pretreatment signs and symptoms or if patient died during or after completion of treatment

II. ***Bacteriologic Response***
   a. *eradication of pathogens* – elimination of candida on post treatment cultures

   b. *failure* – persistence of candida on post treatment culture

   c. *superinfection* – new Candida species isolated on post culture

   f. *adverse drug reactions defined by:* 25% decrease in hemoglobin; 50% or greater decrease in WBC, differential count, or platelets, 3x increase or more in the level of SGPT, SGOT, ALT, AST for age, and 2x or more increase in the BUN or creatinine.

MATERIALS AND METHODS

Charts of 33 patients referred to the Infectious Disease Section and treated for Candida infection with fluconazole from Jan. 1996 to July 1996 were reviewed. Data were entered in a standard data collection sheet.

RESULTS AND DISCUSSION

Fluconazole was given as first line treatment in 33 pediatric patients with culture proven Candida infection. Data gathered showed the age ranged from preterm neonates to 15 years old (see Table 2). Majority of patients 11/33 (34%) were neonates, 50% of which were preterm. The underlying disease conditions are presented in Table 3. Majority of the patients were severely ill with pneumonia (with or without sepsis) compounding other underlying illnesses in 97% of the cases (32/33). 75% of the subjects were intubated. 3/32 very ill patients had leukemia as an underlying disease. Neutropenia at the start of therapy was noted in 3/32 severely ill patients marked with (*). Only 1/33 was stable; a case of ventriculitis with postmeningitic hydrocephalus. An average of 4 broad spectrum antibiotics were used by each patient at the time Candida was isolated. The most common antimicrobial regimen used was a third generation cephalosporin (Ceftazidime 17%) and an aminoglycoside (gentamycin 17%).

Table 2 *Age Distribution of Patients Treated with Fluconazole*

Age	Number of Patients	Percent
<1 month	11/33	34%
1-6 months	7/33	21%
6 mos.-1yr.	2/33	6.25%
>1yr.-3yrs.	4/33	12.5%
4yrs.-9yrs.	5/33	15.6%
14yrs.-15yrs.	3/33	9.3%

Table 3 *Underlying Disease Conditions Associated with Invasive Candida Infection*

DISEASE CONDITION	NO. OF CASES	COMMENTS
sepsis neonatorum with pneumonia	9	*1/9 with WBC - 4.2 improved *1/9 failed therapy, patient had multiple congenital anomalies, isolate was C. krusei
sepsis neonatorum with TEF s/p ligation, with imperforate anus s/p colostomy with gastrostomy, s/p tracheostomy	1	failed therapy expired secondary to complications of 3rd bout of nosocomial pneumonia blood culture C. non albicans
sepsis neonatorum with NEC	1	
sepsis neonatorum s/p end to side esophagostomy tube gastrostomy, s/p tube thoracostomy	1	
1 mo. old with large VSD in failure with sepsis secondary to nosocomial pneumonia	1	failed therapy postmortem blood culture showed Candida sp.
TB menigitis s/p ventriculo-peritoneal shunting with sepsis secondary to nosocomial pneumonia	2	1/2 failed therapy blood cultures grew C. krusei patient requested transfer to a secondary care hospital was moribund on transfer
TB meningitis ill with nosocomial pneumonia	1	
congenital hypoventilation syndrome sepsis secondary to nosocomial pneumonia	1	
obstructive hydrocephalus secondary to an infected dermoid cyst s/p excision s/p ventriculo-peritoneal shunting, infected pseudocyst, neurogenic bladder nosocomial pneumonia	1	
post meningitis hydrocephalus with ventriculitis	1	
meningioma s/p excision nosocomial pneumonia	1	
post infectious demyelinating disease with nosocomial pneumonia	1	
disseminated Kochs with Potts, sepsis secondary to nosocomial pneumonia	1	
disseminated Kochs pulmonary and Potts	1	
cerebral palsy with aspiration pneumonia severe malnutrition	1	
sepsis secondary to gastroenteritis	1	
nosocomial pneumonia	1	
nosocomial pneumonia with sepsis	1	
post-measles pneumonia with sepsis	1	*WBC - 3.0 patient improved
1 1/2y AML M1 sepsis secondary to pneumonia, s/p tracheostomy and chemotherapy	1	*WBC - 1.0 expired failed therapy Candida sp.
AML M1 typhlitis	1	
ALL L3 nosocomial pneumonia	1	
histiocytosis X nosocomial pneumonia	1	

In 66.3% of cases, Candida was isolated from the blood and more than one site (urine or both), with 30% represeting blood isolates along. 33% were isolated from more than one site, 36% of Candida were isolated from the urine. 30% of speciated Candida isolates were *C. albicans*, 15% were speciated as non albicans. Other isolates consisted of *C. parapsilosis* (1/33), *C. glabrata* (1/33), *C. krusei* in 2/33. 14/33 fungal studies were only reported as *Candida sp.*

Fluconazole was administered at 5mg/kg/day single daily dose in 30/33 (90%) and initially at every 2 days for two weeks among 3/33 preterms less than 1 kg. Subsequent dose revision to 3mg/kg/day was done in 2/33 patients. This was secondary to increasing serum transaminases. Both patients, however, were shifted to Amphotericin B. The oral route was preferred in 1/3 (33%) patients. This particular patient had candiduria. The intravenous route was preferred as the initial route in 97% of the cases where candida was isolated from the blood alone, or from the stool and or the urine from very ill patients or from the blood and any other site. The average number of days of therapy was 13.5 days and 13 days when Candida was isolated from 1 or more site, and 7.7 days if isolated from the urine provided repeat cultures were negative.

Laboratory results for AST, ALT, alkaline phosphatase, total bilirubin, BUN, creatinine, hgb, WBC, platelets were requested at baseline and after 7 days. In 2/33 subjects, a continued rise in total bilirubin, AST, ALT, was noted; one patient was a septic neonate (TEF s/p ligation, imperforate anus, s/p colostomy, gastrostomy, thoracostomy for pneumothorax). The other was a 1 1/2-year old with AML M1 with sepsis and neutropenia of 1.0. In both cases, jaundice was present prior to fluconazole and was assessed to be probably secondary to cholestasis from TPN or from sepsis. In both cases Fluconazole was shifted to Ampotericin B. In 1/33 patients who was noted to have increases transaminases, Fluconazole was discontinued after 4 days because of negative cultures and clinical improvement. No adverse changes were seen in the Hgb, WBC, platelet count, BUN/creatinine solely attributed to fluconazole.

Table 4 *Clinical and Mycological Response to Fluconazole Therapy in 33 Evaluated Cases Ages <30 days - 15 years old*

SITE RECOVERED	CLINICAL RESPONSE CURED OR IMPROVED	MYCOLOGICAL RESPONSE ERADICATED
Blood	4/7	7/7
Urine	9/9	9/9
Blood + Urine/Stool or both	16/17	17/17
TOTAL FROM ALL SITES	29/33	33/33

As shown in Table 4, a favorable response was noted in 84% (29/33) cases with both clinical improvement and eradication of Candida. A 100% eradication rate was noted in all *C. albicans* isolates regardless of the site from where it was cultured. Both isolates of *C. glabarata* (1/1) and *C. parapsilosis* (1/1) were eradicated. Only 85% (12/14) of isolates reported as *Candida sp.* were eradicated. An unfavorable response was noted in 15% (5/33) cases with 3 observed mortalities and 1 moribund patient. Only two of the three observed mortalities were, probably, Candida related. All 5 were severely ill. Repeat fungal cultures remained positive despite 5 days of Fluconazole therapy with clinical deterioration. In all cases, Fluconazole was shifted to Amphotericin B. In 2/5 the *Candida sp.* was eventually speciated to *C. krusei*. The remainder of failed Fluconazole cases were composed of Non albicans candidemia 2/5. In one patient, a neonate, Candida infection responded to Amphotericin B, however, he succumbed to complications of a third bout of pneumonia. Another non-albicans Candidemia case involved a septic 30 days old infant with a large VSD complicating a nosocomial pneumonia. Postmortem blood CS grew candida. One case of failure of therapy was a *Candida sp.* in a 1 1/2 yr. old neutropenic AML, M1, who despite 6 days of fluconazole therapy grew *Candida sp.* in the blood. Postmortem lung, and cardiac tap and blood CS grew *Candida sp.* No Fluconazole related fungal superinfection was documented.

Fluconazole, with its good biovailability and minimal toxic effects may be used as an alternative to Amphotericin B as the empiric first line therapy in invasive Candida infection especially where *C. albicans* has been isolated. However, it must be noted that 2-5% of isolates of *C. albicans* may develop resistance to Fluconazole as a result of its repeated or prolonged use. Its prolonged and repeated use may also select the growth of Fluconazole resistant *Candida sp.* Caution and vigilance must be observed when treating critically ill patients with non albicans or cultures reported as *Candida sp.* since Azoles are somewhat less active against many non-Albicans species of candida and related yeasts. (11) *Candida krusei* is highly resistant to Fluconazole. Fluconazole resistance has also been reported in *C. glabrata.* (10) Therefore, every effort must be made to have fungal cultures speciated.

Although there are no strict rules regarding when to repeat cultures, it has been observed that repeat fungal cultures were requested after 5 days of antifungal therapy. It was, however, felt that clinical response should be evident by 72 hours upon initiation of therapy. Amphotericin B should be the first line antifungal in cases of *C. krusei* isolates especially in very ill patients. Likewise, Amphotericin B should be considered in patients being treated for invasive Candidiasis who deteriorate despite 5 days of Fluconazole (where there is no other cause for deterioration). It should also be considered for persistently positive cultures especially when the cultures and non albicans in a patient who does not seem to be improving.

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