Original Articles

DISSEMINATED NOSOCOMIAL CANDIDIASIS IN A PEDIATRIC INTENSIVE CARE UNIT

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ABSTRACT

Nosocomial disseminated candidiasis was diagnosed in 6 out of 200 (3%) children receiving pediatric intensive care over a period of 9 months. The ages of patients ranged between 20 days to 3 years; 4 were < 2 months. Therapy with broad spectrum antibiotics (in all), indwelling cannula (in all), peritoneal dialysis (in 3), low birth weight (in 3) and invasive hemodynamic monitoring were recognizable predisposing factors. The diagnosis was suspected on an average after 14 days, PICU stay (range 8-20 days). All the patients showed a secondary worsening after evidence of improvement from the primary illness. It was characterized by lethargy, fever (in 3), weight loss (in 3), loose stools (in 2) and respiratory distress (in 3), and was indistinguishable from any bacterial sepsis. Presumptive diagnosis was made on basis of KOH wet mount and Gram stained smear findings of mycelia, and was confirmed later on isolation of Candida species from one or more body sites and blood culture. All the patients showed disappearance of symptoms and mycological cure within 6-14 days of oral itraconazole therapy, (10 mg/kg/day in 2 divided doses). The therapy was continued for upto 14 days after sterile fungal blood culture, and was well tolerated. Fungal superinfection especially with Candida must be looked for in hospitalized patients suspected of nosocomial infection. Early oral itraconazole is effective in disseminated candidiasis and well tolerated by children.

Key words: *Candidiasis, Candidemia, Fungal infections, Intensive care, Itraconazole, Nosocomial infections.*

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Candida species are the most prevalent fungi causing deep seated mycoses(l). These normally ubiquitous organisms have been shown to cause a wide spectrum of clinical disease ranging from mucocutaneous infections (*e.g.,* thrush) to fatal disseminated diseases with multiple organ involvement. Low birth weight, prolonged indwelling catheters, broad-spectrum antibiotic therapy and disruption of gastrointestinal mucosa are some of the risk factors for disseminated candidiasis(2). Mortality rates are high in infants with untreated disseminated candidiasis, especially if there is an associated debilitating disease(3). With the growing increase in diagnostic and therapeutic interventions in the intensive care settings, the incidence of systemic fungal infection is likely to as-

sume serious magnitude. Last year we have encountered six cases of disseminated candidiasis over a relatively short period of nine months in our Pediatric Intensive Care Unit (PICU). This paper presents our approach to diagnosis and highlights role of itraconazole therapy in disseminated candidiasis.

Details of Cases

A review of clinical records of PICU revealed that 6 children had disseminated candidiasis from March through December 1993. All were treated with oral itraconazole. For the purpose of this review, disseminated candidiasis was defined as isolation of Candida from the blood together with another body-site in a sick child.

The primary diagnosis and clinical profile of these patients are summarized in *Table I.* The patients ranged in age from 20 days to 3 years and included 2 girls and 4 boys. The mean duration of stay in PICU was 28 days (range 16-38 days). Signs of systemic candidiasis were noticed between day 8 to 20 after hospitalization (median-day 15). Multiple risk factors were present; these were use of broad-spectrum antibiotics (in all), prolonged intravenous catheters (in all), low birth weight (in 3), invasive hemodynamic monitoring (in 2), and peritoneal dialysis (in 3). All the patients showed a secondary worsening after showing clear improvement from the primary illness while receiving broad-spectrum antibacterial therapy. This led to a suspicion of fungal infection in them.

Using a standard protocol, multiple specimens were obtained from oral lesions, tracheal aspirates, stool, urine, catheter sites, skin and blood. Specimens collected from surface lesions of aspirates were studied under direct microscopy on 10% potassium hydroxide (KOH) wet mount, India ink preparations and Gram's stained smear. All the cultures were performed on Sabourad's dextrose agar except that of blood. Blood was inoculated immediately in two sets of biphasic media containing brain-heart infusion agar and broth and identified by standard method(4).

Presence of pseudohyphae or mycelia on smear examination was considered suggestive enough of candidiasis to start empiric oral itraconazole therapy. The diagnosis of disseminated candidiasis was confirmed later on confluent growth of *Candida albicans* from blood and other specimens. Itraconazole was removed from 100 mg capsules and grounded to a fine powder. The requisite amount (10 mg/kg/day) was administered orally in two divided doses dissolved in 10 ml of double distilled water. Repeat fungal blood cultures were obtained at regular intervals. These were sterile after a mean duration of 9.6 days (range 6-14 days). The therapy was continued for up to 14 days after obtaining a sterile fungal blood culture (mean duration 23.6 days, range 21-30 days). Oral itraconazale therapy resulted in rapid clinical improvement in general condition and mycological cure in all the six patients. The drug was generally well tolerated by most patients. Blood counts, electrolytes, and renal and liver functions tests were also monitored during the therapy. These remained within normal limits in all. On follow up examination all the patients were asymptomatic and thriving well.

TABLE I—*Clinical Profile of Six Patients With Disseminated Candidiasis*

Case No.	1	2	3	4	5	6
Age at admission	25 days	40 days	20 days	30 days	8 months	3 years
Primary illness	Organophosphorus poisoning with pneumonia	Vent septal defect S.typhimurium meningitis	Acute gastroenteritis, Renal failure	Acute diarrhoea (S. typhimurium), Renal failure, Pneumonia	Hemolytic uremic syndrome, Pneumonia	Staphylococcal sepsis with endocarditis pyopericarium
Treatment received	Ventilation, Atropine, Ciprofloxacin, Cefotaxime, IV fluids	Cefotaxime, Amikacin, Ciprofloxacin, IV fluids	Peritoneal dialysis, Cefotaxime, IV fluids	Peritoneal dialysis, C. penicillin, Ceftriaxone, Ciprofloxacin, IV fluids	Peritoneal dialysis, Ciprofloxacin, IV fluids	C. penicillin, Cloxacillin, Gentamicin, IV fluids, Invasive monitoring
Response	By day 6 weaned off ventilator	By day 12 afebrile, tolerated feeds, sensorium better	By day 4 renal functions normalised, sensorium improved	On day 4 renal function improved, Resp. distress passive	On day 6 afebrile, accepted feeds, Resp. distress passive	No improvement, Worsened, developed shock, required inotropes and pericardiocentesis
Complicating illness	On day 9 pneumonia, Resp. failure, needed ventilation	On day 20 loose stools, weight loss, fever	On day 8 lethargy, poor feeding, fever	On day 15 loose stools, resp. distress (pneumonia), skin rash	On day 16 fever, Resp. distress (pneumonia)	On day 15 fever, shock
Sites of candida isolation	Blood, tracheal aspirate, urine, stool	Blood, oesophageal aspirate, abscess, urine, stool	Blood, urine	Blood, skin rash, urine, stool	Blood, tracheal aspirate, stool	Blood, urine, stool

TABLE I *(contd.)*–*Clinical Profile of Six Patients With Disseminated Candidiasis*

Case No.	1	2	3	4	5	6
Age at admission	25 days	40 days	20 days	30 days	8 months	3 years
Sterile fungal culture day	10th day	13th day	7th day	14th day	8th day	6th day
Itraconazole (duration)	24 days	27 days	21 days	28 days	22 days	30 days
Response	Weaned off ventilator, X-ray chest normal	Weight gain, control of congestive cardiac failure	Activity improved, weight gain	Resp. distress passive, Loose stools stopped, weight gain	Fever passive, Resp. distress passive	Afebrile, Weight gain
Risk factors	Ventilation, prolonged IV fluids, Broad spectrum antibiotics, Invasive monitoring	Broad spectrum antibiotics, IV fluids	Peritoneal dialysis, low birth weight, broad spectrum antibiotics	Peritoneal dialysis, low birth weight, broad spectrum antibiotics	Peritoneal dialysis, IV cannula, broad spectrum antibiotics	Invasive monitoring, Broad spectrum antibiotics and IV fluids

Discussion

Fungal infection are often not considered in children suspected of nosocomial sepsis because of preponderance of acute bacterial illnesses and nonspecific clinical picture. Nonetheless, fungal infections especially candidiasis may be responsible for serious and occasionally fatal disease in infants and children. These infections occur in a variety of clinical settings. Environmental factors and disturbances in host defense are causative.

Systemic candidiasis is defined as histopathological evidence of Candida infections or isolation of Candida from a normally sterile body site including blood(2,6,7). The incidence varies according to settings in which it is found. It ranges from 0.6-3% in very low birth weight infants(8,9) to 10-15% in -tertiary care centers(l0). Systemic candidiasis is arbitrarily classified into catheter related sepsis and disseminated candidiasis (5). Catheter related infections offer no evidence of dissemination, only blood cultures from central venous catheters (CVC) are positive. Antifungal therapy is recommended(11). Disseminated candidiasis can have evidence of "focality" and positive culture from a sterile site; blood cultures continue to be positive after removing a CVC. All cases from our series would fall into the category of disseminated candidiasis since they all were seriously sick, had evidence of focality and blood cultures obtained from a fresh peripheral venipuncture site grew Candida.

Laboratory diagnosis of disseminated candidiasis poses problems because of difficulties in isolation and interpretation of Candida from various body sites(12). Routine blood cultures are insensitive and nonspecific in diagnosing disseminated candidiasis(12). The sensitivity can be increased by venting aerobic blood culture bottles, using pour plates or by early blind subculturing(13). If Candida is not isolated from the blood, a demonstration of fungus in the joint fluid, cerebrospinal fluid, and pleural or peritoneal fluid by direct microscopic examination or culture establishes the diagnosis(14). Isolation of Candida from oral cavity, sputum, feces or urine may be difficult to interpret because it may be found in these sites in the absence of tissue invasion and clinical disease. Transient candiduria may occur in patients receiving antibiotics, especially in the presence of urinary catheters. However, Candida may also be a cause of significant disease of the urinary tract(15,16). Isolation of Candida in suprapubic urine may be taken as an evidence of systemic or urinary tract candidiasis(l,17). None of our patients had a urinary catheter *in situ* and the specimens were obtained by suprapubic aspiration.

Rapid diagnostic methods which involve detection of antibodies to Candida species have proven insensitive because of difficulty in distinguishing colonization from deep seated infections and nonspecificity in immunocompromised patients(18). Because of the problems with antibody detection, antigen assays utilizing latex agglutination (CAND-Tec) (19), enzyme immunossays and detection of metabolites produced by Candida such as arabimitol(20) provide future promise.

Of the recognized predisposing fac-

tors for disseminated candidiasis those present in our patients were broad spectrum antibiotic therapy, prolonged intravenous catheters *in situ,* peritoneal dialysis, low birth weight (LBW), and invasive hemodynamic monitoring. In recent years increasing survival of LBW babies have resulted in an increased incidence of candidiasis in them(8,21,22). Increased susceptibility to infection with Candida in patients receiving broad spectrum antibiotic therapy(23) is attributed among others to antibiotic induced suppression of normal bacterial flora, direct stimulatory effects and removal of competition for nutrients. CVCs increase risk for candiclemia(5) as infection at catheter exit site or along the tunnel tract may progress into candidemia(24). With growing use of these catheters, the incidence of Candida infection is likely to increase(4,13,23,25). Three of our patients had undergone peritoneal dialysis. Peritonitis due to Candida occurs most often in patients receiving chronic ambulatory peritoneal dialysis(26) but dissemination is rare. A chance contamination of peritoneal dialysate in our patients was ruled out by negative fungal cultures of the dialysate.

Clinically there are no specific pointers to the diagnosis of disseminated candidiasis although Candida does appear to affect certain organ systems more than others especially lungs(25), kidney(16,17), and the meninges(27). In infants who have sites of infection secondary to fungemia, signs and symptoms of secondary foci may prevail. Pneumonia as seen in our cases 1, 4 and 5 occurs most commonly by disseminated disease and not by aspiration(25) but it presents an array of radiologic pattern with no characteristic findings to distinguish them from any other acute or chronic pulmonary infection(25).

We have treated all our cases of disseminated candidiasis with oral itraconazole, which is one of the promising newer and safer antifungal drugs with demonstrated broad- spectrum activity (6,28,30). In an experimental study by Vancustem *et al*.(6), itraconazole proved superior to oral and parenteral fluconazole, and parenteral amphotericin-B. Of 55 adults with systemic candidiasis, 69% were cured or markedly improved by oral itraconazole at a mean dose of 200 mg once daily for a mean of 1 month(30). Information about itraconazole therapy of disseminated candidiasis in infants is limited. Bhandari *et al*.(31) used oral itraconazole successfully in a dose of 10 mg7kg/day for treatment of systemic candidiasis in a very low birth weight nebnate. Most common side effects are mild gastrointestinal complaints such as nausea, anorexia, cramps and flatulence(30). Asymptomatic increase in liver enzymes have been documented in 1 to 2% of patients(32). However, dosage adjustment is not required in patients with renal or hepatic impairment(32). Our patients were too young to complain of above side effects. Apparently, the drug was well tolerated by all; none had any abnormality of electrolytes, renal functions and liyer functions during the entire duration bf therapy.

To conclude, fungal superinfection especially with Candida must be looked for in patients suspected of nosocomial infection in PICUs. Early oral itraconazole which was effective and safe in our limited experience may be a wel-

come addition to the limited range of existing antifungal drugs for oral use.

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