PEDIATRIC NOSOCOMIAL FUNGAL INFECTIONS

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Abstract. During a period of twelve years (1984-1995), ninety-seven pediatric patients experienced 107 nosocomial fungal infections at Mackay Memorial Hospital. The nosocomial fungal infection rate in pediatric patients was lower than that of the hospital as whole, but it increased significantly. The average rate in the last three years (1993-1995) was 1.20 per thousand discharged patients, 10 times that of the first three years (1984-1986). Two-thirds of the patients were below one year of age. Half of the infections occurred in Intensive Care Units. The bloodstream was the most common site of infection (40.2%), followed by the urinary tract and skin. Important underlying diseases included malignancies, prematurity, and congenital anomalies. Common risk procedures included total parenteral nutrition (43.3%), endotracheal intubation (29.9%), central venous catheterization (25.8%), operation (14.4%). Near 90% of the patients had previously received antibiotics. *Candida albicans* was responsible for 58.1% of the infections. Thirty-three patients expired, of whom 18 died of the fungal infections. With the trend of increasing nosocomial fungal infections, physicians should be more alert to the possibility of such infections.

INTRODUCTION

A few decades ago, fungi were rarely isolated as hospital-acquired pathogens (McGowan *et al*, 1975). However, they have recently emerged as important pathogenic agents (Bodey, 1988). Nosocomial fungal infection rates vary on different services. The lowest rates are reported in obstetric, newborn, gynecologic, and pediatric services; the highest rates are in burn, trauma, cardiac surgery, oncology, high risk nursery, and general surgery units (Beck-Sague and Javis, 1993). Unfortunately, the incidence is increasing across the board. Nosocomial fungal infections, especially fungemia, are associated with very high mortality (Wey *et al*, 1988; Fraser *et al*, 1992). To reduce the high mortality, early detection and management are mandatory.

In this hospital, the pediatric service has 306 beds, including 33 beds in the neonatal Intensive Care Unit, 14 beds in the pediatric Intensive Care Unit, 70 beds in the intermediate care nursery, 68 beds on the general pediatric ward, 26 pediatric surgery beds, and 95 nursery beds. Patients include normal newborns and children with all kinds of pediatric diseases, *eg* prematurity, infectious, respiratory, cardiac, neurologic, hemato-oncologic, urogenic, endocrinologic, and surgical problems. Approximately eight thousand patients are discharged from these pediatric wards each year. This report reviews nosocomial fungal infections during the past twelve years on the pediatric service.

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MATERIALS AND METHODS

From January 1984 to December 1995, all patients admitted to the Department of Pediatrics of Mackay Memorial Hospital underwent surveillance for nosocomial infection. That data was retrospectively reviewed for this report. The definition of nosocomial infections in this hospital is based on the guidelines of the Centers for Disease Control (CDC, USA) (Garner *et al*, 1988).

One member of the Infection Control Committee, in charge of the pediatric wards, reviewed all the pediatric charts and collected positive culture results from the microbiological laboratory. Any infections fulfilling the criteria for nosocomial infection and in which positive fungal cultures were found was included in this study. Data compiled included the patient's age, sex, date of admission, date of acquisition of fungal infection, ward on which the infection was acquired, infection site, underlying disease, invasive or specific procedures, usage of antibiotics, corticosteroids, chemotherapeutic agents for malignancy, antifungal agents,

and final outcome.

The presumed onset of infection was defined as the date of developing fever, signs of infection, or significant clinical deterioration. Risk procedures included intravascular and urinary catheterization, parenteral nutrition, endotracheal intubation, blood exchange transfusion, dialysis, and operation within two weeks prior to onset of fungal infection. The use of the following medicines was considered to be a risk factor: antibiotics, within 48 hours; corticosteroids, for at least one week; and chemotherapeutic agents, within two weeks before fungal infection. In fatal cases, the death was considered as caused by fungal infection if the patient's condition deteriorated after onset of the fungal infection and/or there was absence of a more likely cause of death.

RESULTS

During this twelve-year period, nosocomial fungal infection rates significantly increased (Fig 1). The average fungal infection rates from 1984 to 1986 were 0.95 per thousand discharged patients for the entire hospital and 0.12 for the pediatric wards. These rates increased from 1993 to 1995 to 5.25 per thousand discharged patients for the entire hospital and 1.20 for pediatric wards; this represented a 5.5-fold increase for all hospitalized patients, and a 10-fold increase for pediatric patients.

During this period, there were 97 pediatric patients with 107 episodes of nosocomial fungal infections. Eighty-seven patients had a single infection, seven had two infections, and two had three

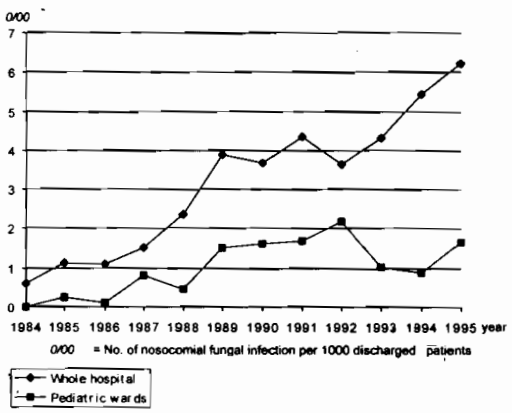

Fig 1–Nosocomial fungal infection rates from 1984 to 1995 at Mackay Memorial Hospital.

infections. Fifty-eight patients (59.8%) were male and 39 (40.2%) were female. Nearly two-thirds were below one year of age (Table 1). Near half of the patients (49.5%) acquired their infections in Intensive Care Units, the remainder (50.5%) on the general wards.

The bloodstream was the most frequent site from which fungi were cultured, followed by the urinary tract and skin (Table 2). The most important underlying diseases were leukemia or other malignancies (15 cases, 15.5%), prematurity (14 cases, 14.4%), and congenital anomalies (13 cases, 13.4%). Total parenteral nutrition, endotracheal intubation, central venous catheterization, operation, umbilical artery catheterization, and urinary catheterization were the most common procedural risk factors (Table 3). Nearly 90% of the patients had received antibiotics (Table 3); for longer than one week in 80.6%, and longer than two weeks in 41.4%. These patients received on an average 2.2 different antibiotics. The average length of admission before fungal infection was 32.2 ± 19.8 days.

Among 43 episodes of fungemia, the most commonly isolated pathogen was *Candida albicans*

Table 1

Age distribution of 97 nosocomial fungal infection patients.

Age	No. of patients	%
< 1m/o	20	20.6
1-12 m/o	42	41.3
1-4 y/o	14	14.4
5-15 y/o	21	21.6

Table 2

Infection sites of 107 nosocomial fungal infections.

Sites	No. of infections	%
Bloodstream	43	40.2
Urinary tract	26	24.3
Skin and soft tissue	20	18.7
Others	18	16.8

Table 3

Risk factors in 97 nosocomial fungal infection patients.

Risk fators	No. of patients	%
Procedures		
Total parenteral nutrition	42	43.3
Endotracheal intubation	29	29.9
Central venous catheterization	25	25.8
Operation	14	14.4
Umbilical artery catheterization	11	11.3
Urinary catheterization	10	10.3
Arterial catheterization	5	5.2
Hemodialysis	2	2.1
Blood exchange transfusion	1	1.0
Medications		
Antibiotics	87	89.7
Corticosteroids	14	14.4
Chemotherapeutic agents	12	12.4

Table 4

Fungi isolated in 43 patients with fungemia.

Fungi isolated	No. of patients	%
Candida albicans	25	58.1
C. tropicalis	4	9.3
C. krusei	3	7.0
C. parapsilosis	3	7.0
C. pseudotropicalis	2	4.7
C. guilliermondii	1	2.3
C. glabrata	1	2.3
Unidentified yeast	4	9.3

(58.1%); other identified non-albicans *Candida* species accounted for 32.6% (Table 4). Of these 43 fungemic patients, 15 (34.8%) were fatal; 11 (25.6%) were caused by fungal infections.

Of the 97 patients with fungal infections, 33 (34.0%) patients expired; 18 (18.6%) died as a result of their fungal infections. Among the 18 fungal infection-related fatalities, 11 patients had fungemia, 6 had funguria, and one had fungus isolated from a central venous catheter tip. Fifteen of these patients had received antifungal therapy within an average of 4.13 ± 2.07 days after onset of infection. Six received both amphotericin B and fluconazole, eight received amphotericin B, and one received fluconazole only.

DISCUSSION

Fungi are currently one of the most rapidly emerging groups of nosocomial pathogens. In the United States, different sizes of hospitals had increases of 75 to 487% in the rate of nosocomial candidemia from 1980 to 1989 (Banerjee *et al*, 1991). In Taiwan, National Taiwan University Hospital experienced a 27-fold increase in candidemia from 1980 to 1994 (Hung *et al*, 1996). This hospital has had the same increasing trend. On the pediatric wards, although the fungal infection rate is lower than in the hospital as a whole, the rate of increase is greater.

Factors contributing to this increasing trend include the use of broad-spectrum antibiotics, long-term indwelling catheters, chemotherapy for malignancy, major operations, etc (Karabinis *et al*, 1988; Bross *et al*, 1989). As is so often the case, medical progress has provided improved treatment for serious clinical conditions, but at the cost of increased risks of serious side effects, such as fungal infections.

The age distribution of our infected patients may simply reflect the age distribution of the pediatric inpatient population here. However, patients in Intensive Care Units have a higher rate of infection, caused not only by their medical condition but also related to the environment. Several outbreaks of fungal infections in neonatal Intensive Care Units have been reported (Baley *et al*, 1986; Weese-Mayer *et al*, 1987; Bulter and Baker, 1988), but there were no such episodes in Intensive Care Units here during the study period.

It is difficult to define invasive fungal infection. Fungemia may represent a true systemic infection or be just a transient, self-limiting condition. Further complicating the issue is that blood cultures infrequently yield the organism even in disseminated fungal infections (Klein and Watanakunakorn, 1979). Funguria does not prove renal involvement. Conversely, kidney or liver fungal infections may not cause abnormal renal or hepatic function tests (Hughes, 1982). Fungi were most commonly isolated from blood and urine in our study. According to the CDC definition, clinical findings are important to invoke the diagnosis of nosocomial infection. However, clinical symptoms and/or signs are usually nonspecific and subtle in children especially neonates. It is particularly difficult in this

age group to determine whether positive fungal cultures represent invasive infection or not. Since almost all of our urine specimens were collected by suprapubic puncture, false positives from perineal contamination is unlikely. But the clinical significance of these results is still open to question.

It is well documented that immunocompromised patients are susceptible to fungal infections (Karabinis *et al*, 1988; Bross *et al*, 1989). Underlying diseases in pediatric patients are somewhat different from those in adults. In addition to hematological malignancies and solid tumors, prematurity and congenital anomalies are frequently encountered (Baley *et al*, 1986; Weese-Mayer *et al*, 1987; Lee *et al*, 1991). As with adults, invasive procedures, *ie* hyperalimentation, endotracheal intubation, intravascular and urinary catheterization, etc, increase the possibility of fungal infections (Fuchs *et al*, 1984; Solomon *et al*, 1984; Weese-Mayer *et al*, 1987). Some treatments, *ie* antibiotics, corticosteroids, chemotherapy, major operations, and dialysis also increase the risk (McGowan, 1985). A prolonged hospital stay is another contributing factor (Wey *et al*, 1988). These patients had been hospitalized for an average of nearly one month before acquiring a fungal infection; they remained hospitalized for nearly another one month afterward. By contrast, the average duration of hospitalization for pediatric patients overall during the study period was only 7.1 days.

Candida albicans is the most frequently isolated pathogen in nosocomial fungal infections, followed by other *Candida* species (Beck-Sague and Jarvis, 1993). Patients with *Candida albicans* infections may have lower mortality than with non-albicans *Candida* species infections (Fraser *et al*, 1992). Some non-albicans *Candida* species are reported to be associated with specific conditions: *eg C. tropicalis* with leukemia (Wingard *et al*, 1979); *C. parapsilosis* with indwelling catheters, hyperalimentation and solid tumors (Plouffe *et al*, 1977; Meuniser-Corpentier *et al*, 1981); and *C. glabrata* with solid tumors and nononcological diseases (Meuniser-Corpentier *et al*, 1981). However, many of the species-specific findings may merely reflect the period in which the studies were done and the microflora common at each institution, rather than an etiology association (Fraser *et al*, 1992). In this study, such species-specific associations were not found. As in other reports (Beck-Sague and Jarvis, 1993), non-*Candida* fungi were rarely isolated as pathogens in nosocomial infections.

In this study, fungal infection as a cause of mortality occurred in 18.6% of all cases and 25.6% of fungemia, lower than in reports of a series of adult patients (Wey *et al*, 1988; Fraser *et al*, 1992; Hung *et al*, 1996). The difference may be explained by the use of fewer invasive procedures, less use of corticosteroids and chemotherapy in the patients, and the different types of underlying diseases for children and adults.

In summary, pediatric nosocomial fungal infected patients had risk factors similar to adults, but a slightly different pattern of underlying diseases. Infection rate and mortality were lower than that for adults, but the increasing incidence of fungal infection was similar. Fungi have become important pediatric nosocomial pathogens.

REFERENCES

Baley JE, Kliegman RM, Boxerbaum B, Fanaroff AA. Fungal colonization in the very low-birth-weight infants (< 1,500 gms). *Pediatrics* 1986; 78 : 225-32.

Banerjee SN, Emori TG, Culver DH, *et al*. Secular trends in nosocomial primary bloodstream infections in the United States, 1980-1989. *Am J Med* 1991; 91 (suppl 3B) : 865-95.

Beck-Sague CM, Jarvis WR. The National Nosocomial Infections Surveillance System: secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. *J Infect Dis* 1993; 167 : 1247-51.

Bodey GP. The emergence of fungi as maior hospital pathogens. *J Hosp Infect* 1988; 11 (suppl A) : 411-26.

Bross J, Talbat GH, Maislin G, *et al*. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. *Am J Med* 1989; 87 : 614-20.

Bulter KM, Baker CJ. Candida: an increasingly important pathogens in the nursery. *Pediatr Clin North Am* 1988; 35 : 543-63.

Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. *Clin Infect Dis* 1992; 15 : 414-21.

Fuchs PC, Gustafson ME, King JT, Goodall PT. Assessment of catheter-associated infection risk with the Hickman right arterial catheter. *Infect Control* 1984; 5 : 226-30.

Garner JS, Jarvis WR, Emori TG, *et al*. CDC definition

for nosocomial infections. *Am J Infect Control* 1988; 16 : 128-40.

Hughes WT. Systemic candidiasis: a study of 109 fatal cases. *Pediatr Infect Dis* 1982; 1 : 11-8.

Hung CC, Chen YC, Chang SC, Luh KT, Hsieh WC. Nosocomial candidemia in a university hospital in Taiwan. *J Formos Med Assoc* 1996; 95 : 19-28.

Karabinis AS, Hill C, Leclercq B, *et al.* Rick factors for candidemia in cancer patients: a case-control study. *J Clin Microbiol* 1988; 26 : 429-32.

Klein JJ, Watanakunakorn C. Hospital-acquired fungemia: its natural course and clinical significance. *Am J Med* 1979; 67 : 51-8.

Lee W, Burnie JP, Mathews RC, Oppenheim BO, Damani NN. Hospital outbreaks with yeasts. *J Hosp Infect* 1991; 18 (suppl A): 237-49.

McGowan JE Jr. Changing etiology of nosocomial bacteremia and fungemia and other hospital-acquired infections. *Rev Infect Dis* 1985; 7 Suppl 3 : S357-70.

McGowan JE Jr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935-1972), with special reference to hospital-acquired cases. *J Infect Dis* 1975; 132 : 316-35.

Meuniser-Corpentier F, Kiehn TE, Armstrong D. Fungemia in the immunocompromised host: changing patterns, antigemia, high mortality. *Am J Med* 1981; 71 : 363-70.

Plouffe JF, Brown DG, Selva J Jr, Elk T, Stricof RL, Fekety FR Jr. Nosocomial outbreak of *Candida parapsilosis* fungemia related to intravenous infusions. *Arch Intern Med* 1977; 137 : 1686-9.

Solomon SL, Khabbaz RF, Parker RH, *et al.* An outbreak of *Candida parasilosis* bloodstream infections in patients receiving parenteral nutrition. *J Infect Dis* 1984; 149 : 98-102.

Weese-Mayer DE, Fondriest DW, Brouillette RT, Shulman ST. Risk factors associated with candidemia in the neonatal intensive care unit: a case-control study. *Pediatr Infect Dis J* 1987; 6 : 190-6.

Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia: the attributable mortality and excess length of stay. *Arch Intern Med* 1988; 148 : 2642-5.

Wingard JR, Merz WG, Saral R. *Candida tropicalis*: a major pathogen in immunocompromised patients. *Ann Intern Med* 1979; 91 : 539-43.