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Systemic neonatal candidiasis

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SUMMARY

Forty-five cases of systemic neonatal candidiasis were diagnosed over a 9-year period in a neonatal intensive care unit; 42 infants weighed less than 1·5 kg. All had been very ill with preceding bacterial sepsis and other complications of low birthweight. Where treatment was instituted the mortality was low (4 out of 39 dying) and complications of treatment were transitory. We therefore recommend diligent examination for the presence of this infection, and treatment with a combination of amphotericin B and 5-flucytosine.

INTRODUCTION

Sepsis remains an important cause of morbidity and mortality in the newborn infant; especially so in infants of low birth weight requiring intensive care.[1] Systemic candidiasis has become recognised as a significant cause of sepsis in our unit over the past 9 years, and we have therefore analysed data on the 45 cases that have occurred during that period.

METHODS

Forty-five patients were diagnosed over a 9-year period (July 1980 — July 1989) as having systemic candidiasis in the Neonatal Intensive Care Unit, Royal Maternity Hospital, Belfast. The diagnosis was established by the culture of candida from venous blood and/or the finding of budding yeasts in urine obtained by suprapubic aspiration, followed by subsequent culture of candida. Cases diagnosed at postmortem by the finding of candidal abscesses in lung, brain, heart and liver were included where the diagnosis had not been made antemortem.

RESULTS

Forty-five infants (Table) were found to have systemic candidiasis. All were pre-term, and less than 35 weeks gestation. Twenty-three were very immature, being $\leqslant$ 27 weeks gestation. Consequently the babies were small and 20 weighed less than 1·0 kg. All the infants prior to the diagnosis of candidiasis had been very ill

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TABLE

Clinical details on 45 infants with systemic candidiasis

	Mean	Range
Gestation (weeks)	27·7 ± 2·3	25 – 34
Weight	1105 ± 342	537 – 2440
Age at diagnosis (days)	35 ± 20	9 – 80
Positive cultures:		
Blood	36	
Urine	27	
Blood and urine	19	
CSF	6	
Complicating disease:		
Bronchopulmonary dysplasia	16	(37%)
Patent ductus arteriosus	17	(40%)
Congenital malformation	3	(7%)

with proven bacterial sepsis, the majority (84%) with staphylococcal septicaemia (*Staphylococcus aureus*). All had received at least three courses of antibiotics, with a mean of 5·5 courses. Forty (93%) had received cephalosporin treatment as part of the antibiotic therapy. All had received periods of assisted ventilation in the treatment of respiratory failure secondary to respiratory distress syndrome, pulmonary immaturity or pneumonia. Many had complications including bronchopulmonary dysplasia or patent ductus arteriosus, prolonging their inpatient stay, and increasing their morbidity. The great majority had the diagnosis made on blood culture, and a number also had yeasts seen on direct examination of the urine prior to culture. Less than half had combined positive urine and blood cultures.

With the exception of those babies who were diagnosed at postmortem, the mean age at diagnosis was 35 ± 20 days with a range from 9 – 80 days. All the infants had at some time arterial catheters, either umbilical or radial, *in situ,* but only three infants had arterial catheters *in situ* at the time of diagnosis. Although all infants were receiving intravenous feeding none had central catheters present at the time of diagnosis.

There were 10 deaths. The diagnosis was established in five infants at postmortem; these infants were the first in our series and in one, although fungi were found in tissues at postmortem, the main cause of death was a coliform meningitis; the other four infants probably died from the effects of disseminated candidiasis, the organism being found widely spread throughout lung, brain, heart and liver. Of the other infants who eventually died following clinical and laboratory diagnosis of infection, two died from respiratory failure secondary to bronchopulmonary dysplasia, one from a complex cardiac malformation, one from sudden infant death syndrome after discharge from hospital, and one from candidiasis.

The incidence of infection increased during the nine-year period reaching a maximum of 10 cases in 1987. The most frequent presenting sign was apnoea, seen in 21 infants, while in a further 21 the combination of lethargy, temperature instability, colour change and hyperglycaemia was also seen. Seven presented with abdominal distension, three with sclerema; most infants had more than one sign or symptom.

The infants were treated with a combination of amphotericin B between 0·1–0·5 mg/kg/day and flucytosine 100 mg/kg/day in two divided doses. The mean length of treatment was 18 days, ranging from 1–42 days. None suffered any obvious severe acute or long-term toxic effects from these drugs, with the exception of a transient rise in liver enzymes in 15, and in a further eight a fall in platelet count below 100,000 cu mm during periods of treatment. Amphotericin B and 5-flucytosine levels were assayed, but levels above therapeutic recommendations were not detected. Where treatment was instituted the outcome was relatively satisfactory, in that only four of the 39 infants that were treated died. One infant was not treated in view of his moribund state. On examining the cause of death of those babies who died, it is probable that only one died from candidiasis, the others dying some time after the infection had been eliminated, and from some other disease or pathological condition.

Twenty-four of the 41 infants were known to be colonised with *Candida spp.* prior to the diagnosis of systemic spread, a higher proportion than that found by Faix et al.[2] Five of our patients were colonised at birth and the remainder in the subsequent two weeks. Therefore we now treat all infants in long-term intensive care with oral nystatin routinely where *Candida spp.* has been grown from superficial swabs.

All the surviving infants have been followed up as outpatients. The oldest child at the time of the last examination was aged 6 years and the youngest less than 6 months. Of the 29 infants of more than one year of age, 23 appeared to be making adequate physical and developmental progress, four had moderate developmental delay and two had cerebral palsy; whether these problems can be attributed to candidiasis or other complications occurring during the perinatal period is impossible to say.

DISCUSSION

Systemic candidiasis represents an important cause of morbidity and mortality in our patients. It occurred in approximately 0·5% of low birth weight infants, but was found in 11% of those weighing less than 1·0 kg. Very low birth weight has also been recognised as important by Johnson et al[1] and Faix et al.[2] The signs and symptoms observed in these babies mimic bacterial sepsis, emphasising the importance of routine fungal as well as bacterial culture in the investigation of possible sepsis in infants of low birth weight, particularly those weighing less than 1·5 kg.

It is encouraging that despite using drugs thought to be potentially toxic in adults, none of the infants appeared to have suffered long-term ill-effects from amphotericin or flucytosine. Some infants may have had transient hepatic and haematological changes, but these findings may be related rather to the infection than to the medication given. Smith and Congdon[3] have commented on the

difficulty of obtaining positive blood cultures, but we found the reverse: there were more infants with positive blood cultures than with positive urinary findings. A minority had both positive urine and blood findings. It remains to be seen whether routine treatment with oral nystatin will significantly reduce the incidence of local or systemic candidiasis either by its removal from the gut after birth, or by reducing the incidence of cross-infection. At present we start treatment with nystatin in those infants from whom *Candida spp.* are cultured and who are in need of intensive care.

The main factors predisposing to infection in these infants appear to be their low birth weight, their associated immunological immaturity and the breaching of their physical defences following long periods of intensive care, during which they undergo invasive treatments such as artificial ventilation and vascular catheterisation. The infants in our series who developed this infection were a more ill group than the other infants treated in the unit over the same period; 100% required ventilation as against 43%; 37% had bronchopulmonary dysplasia against 17%, and 40% had patent ductus arteriosus against 13% of the comparative population. Despite the fact that 20 of these babies were less than 1 kg, 14 survived, a rate similar to babies weighing less than 1 kg who were cared for in the ward during the period under consideration.

We see little prospect of this infection being eliminated, in view of the increasing numbers of low birth weight infants at present surviving. Long periods of intensive care, due to the development of more sophisticated methods of treatment, including better perinatal management and surfactant administration is the major risk factor. We suggest that a high degree of awareness be maintained regarding the possibility of this infection, and that the appropriate examination and cultures of specimens from patients who may present with the rather vague clinical signs and symptoms described be carried out. Where possible, vascular catheterisation should be avoided, and most important of all, antibiotics should be given only under sound bacteriological advice for minimal periods of time. The Editor of the Year Book of Pediatrics (1986)[5] commented laconically "Some of these infants of extremely low birth weight remain in the nursery so long, is it any wonder that they become mouldy?"

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