a superimposed nutritional deficiency which further impairs their resistance, especially to diarrhoeal disease. This suggests that one important cause of postneonatal mortality in Latin America is low birthweight, possibly as a result of poor maternal health and nutritional status. In other parts of the world—for example in Africa and the Indian sub-continent—the prevalence of low birthweight is considerably higher than in Latin America.

The purpose of this report is to stress the need for more information concerning the age distribution of infant deaths. The available data indicate that about 80% of infant deaths in developing countries are occurring in the first 6 months of life. If this is so, much greater attention must be given to the very young infant if the problem of high infant mortality is to be tackled effectively.

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Correspondence to Dr Ann Ashworth, Department of Human Nutrition, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT.

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Neonatal systemic candidiasis: a failure to respond to intravenous miconazole in two neonates

P N MCDUGALL, P J FLEMING, D C E SPELLER, P DAISH, AND B D SPEIDEL

Department of Child Health and Department of Microbiology, Bristol Maternity Hospital

SUMMARY Two extremely preterm infants undergoing intensive care who developed systemic candidiasis are reported. Each was treated initially with intravenous miconazole. One child initially responded, but relapsed after the miconazole was stopped. The second child showed evidence of progression of the disease during treatment. Both infants responded to a combined course of amphotericin B and 5-fluorocytosine. We consider that miconazole is not the drug of first choice in the treatment of neonatal systemic candidiasis.

Systemic candidiasis is a well-known complication in sick preterm infants needing intensive care. The prognosis for such infants, particularly those with *Candida meningitis*, is poor and there is a high incidence of neurological sequelae in survivors.^{1,2} We report two infants with systemic candidiasis who failed to respond to treatment with intravenous miconazole.

Case 1

A boy, birthweight 1000 g, was born by spontaneous vaginal delivery at 26 weeks' gestation. His neonatal course was complicated by respiratory distress syndrome, severe apnoea, a pulmonary haemorrhage, sclerema, and patent ductus arteriosus. He required respiratory support via an endotracheal tube for 68 days and received intravenous nutrition for 70 days. He was given 4 courses of broad spectrum antibiotics (penicillin and gentamicin) for suspected sepsis.

On day 36 his condition deteriorated. Blood and urine cultures showed a heavy growth of *Candida albicans*. Cerebrospinal fluid (CSF) was normal with no growth of organisms on culture. Intravenous miconazole, 15 mg/kg a day in 2 divided doses, was started on day 40. The treatment was stopped on day 50 when his condition had improved and blood, urine, and CSF cultures were negative.

On day 61 his condition again deteriorated with

increasing episodes of apnoea. Blood cultures were negative, but urine cultures showed a heavy growth of *Candida* sp. CSF examination showed $0.39 \times 10^9/l$ white cells with 80% lymphocytes, and *C. albicans* was grown on culture. On day 62 intravenous miconazole was restarted and 3 mg miconazole was instilled into each lateral ventricle on days 62, 63, and 64. The minimal inhibitory concentration (MIC)³ for miconazole was estimated to be 4 mg/l. The strain was shown to be sensitive to 5-fluorocytosine, which was started on day 65 in a dose of 250 mg/kg a day in 4 divided doses given intravenously.

On this regimen the baby's condition improved and subsequent blood, urine, and CSF cultures were negative. Treatment was stopped on day 75.

His condition again deteriorated and CSF cultures on days 99 and 104 both yielded *C. albicans*. Treatment was therefore restarted on day 104 with oral 5-fluorocytosine and amphotericin B. The amphotericin B was given intravenously in daily incremental doses to a maximum of 0.64 mg/kg a day. Ventricular taps were performed on alternate days and 5 µg amphotericin B was instilled into each lateral ventricle. An Ommaya reservoir was inserted on day 120 to facilitate instillation of the amphotericin B.

On day 122 he developed oliguria with hyperkalaemia and hyponatraemia. The intravenous amphotericin B was stopped and renal function rapidly returned to normal. It was restarted on day 131 in daily incremental doses to a maximum of 0.5 mg/kg a day. There were no further complications of the treatment.

Six days after starting the combined treatment all cultures were clear and there was no subsequent growth. His condition improved steadily and the CSF white cell count fell to normal. The intravenous amphotericin B was stopped on day 140 after a total dose of 25 mg and 5-fluorocytosine was stopped on day 150. The intraventricular amphotericin B was stopped on day 150 and the reservoir was removed on day 195.

His subsequent progress has been followed closely and when seen recently for review at age 3 years he was developing normally.

Case 2

A boy, birthweight 800 g, was born by spontaneous vaginal delivery at 26 weeks' gestation. His neonatal course was complicated by birth asphyxia, severe apnoea, bacterial sepsis, patent ductus arteriosus, and pneumonia. He required respiratory support for 64 days and received intravenous nutrition for 40 days. He was given three separate courses of

broad spectrum antibiotics (penicillin and gentamicin) for suspected and proved sepsis.

On day 34 his condition deteriorated with increased ventilatory requirements. A chest x-ray film showed bilateral patchy consolidation. Blood and urine cultures on days 34 and 38 yielded *C. albicans*. CSF examination on both occasions showed no abnormalities. Treatment was started on day 38 with intravenous miconazole 20 mg/kg a day.

On day 42 he developed dactylitis affecting the 3rd and 4th fingers of his right hand and also an abscess on his forehead which yielded *C. albicans*. Neither of these improved with continuing treatment with miconazole. On day 45 he had evidence of increased growth of *C. albicans* in the urine, while blood cultures and the CSF remained clear.

Therefore the miconazole was stopped and he was started on combined treatment with oral 5-fluorocytosine (150 mg/kg a day in 4 divided doses) and intravenous amphotericin B (in daily incremental doses to a maximum of 0.8 mg/kg a day). By day 50 his condition was considerably better and urine, blood, and CSF cultures were clear. The dactylitis and abscess had resolved. All subsequent cultures remained clear. There were no complications of the treatment which was stopped on day 80 after a total dose of 20 mg of amphotericin B.

He developed hydrocephalus which was treated by a ventriculoperitoneal shunt, inserted at age 10 months.

When last seen at 18 months past term he was considered to be performing at a 15 months level, with no gross neurological deficit.

Discussion

There have been reports of the successful use of the combination of amphotericin B and 5-fluorocytosine in the newborn period.^{1,2} However, the toxicity of the former and the development of resistance to the latter have prompted a search for a safer and a more reliable alternative.

The successful use of miconazole in the treatment of systemic fungal infections has been widely reported in adults⁴ and neonates.^{5,6} Its advantages have been considered to be its low toxicity and broad spectrum of *in-vitro* activity against Gram-positive cocci and most fungi and yeasts.

Both of our patients showed some of the problems of the management of systemic candidiasis in the newborn period. Case 1 appeared to respond initially to miconazole but relapsed after treatment was stopped. A further course failed to eradicate the organisms. The MIC observed for the candida isolate after treatment with miconazole (measured by standard methods at the Mycological Reference

Laboratory, London School of Hygiene and Tropical Medicine),³ suggested the development of resistance. Values obtained for MIC of imidazole compounds however, are highly dependent on *in-vitro* conditions⁷ and it is not at present possible to relate them with certainty to results *in vivo*. It would appear that the most effective way of monitoring the response to miconazole treatment is the clinical condition of the patient and the absence of *Candida* sp. from cultures.

Case 2 showed clinical evidence of progression of the disease during the course of treatment with miconazole.

Both patients responded well when the treatment was changed to a combination of amphotericin B and 5-fluorocytosine, with laboratory evidence that the organisms were highly sensitive to these drugs. Studies *in vitro* have shown a synergistic effect between amphotericin B and 5-fluorocytosine.⁸ We consider that this combination is the treatment of choice in neonatal systemic candidiasis and that miconazole should be reserved for those instances where there is a failure of response or significant side effects to either drug.

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Correspondence to Dr P J Fleming, Department of Child Health, Bristol Maternity Hospital, Southwell Street, Bristol BS2 8EG.

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Energy balance, nitrogen balance, and growth in preterm infants fed expressed breast milk, a premature infant formula, and two low solute adapted formulae
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Liver disease in India
S A Bhawe, A N Pandit, A M Pradhan, D G Sidhaye, A Kantarjian, A Williams, I C Talbot, and M S Tanner

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