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Neonatal systemic candidiasis

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SUMMARY Ten babies who required neonatal intensive care developed systemic candidiasis. Eight were extremely preterm (28 weeks' gestation or less) and all received prolonged ventilation, multiple courses of broad spectrum antibiotics, and intravenous hyperalimentation. Diagnosis was established by culture of yeasts from suprapubic urine specimens; venous blood cultures proved unreliable. Initial treatment with 5-flucytosine alone in eight babies and combined with amphotericin B in two, eradicated the infection in nine babies, the treatment failure arising through diagnostic delay and development of resistance to 5-flucytosine. Prophylactic topical antifungal drugs, regular screening of suprapubic urine specimens, and prompt use of systemic antifungal agents before multifocal infection becomes established may reduce the incidence and improve outcome.

Infection with unusual organisms is an increasing problem in neonatal intensive care units and presents new challenges to the neonatologist and microbiologist.[1] Systemic candidiasis causes particular problems, both in its presentation, which may be indistinguishable from bacterial septicaemia, and in the choice of treatment, which must be both effective and non-toxic. In addition, the high incidence of skin and gastrointestinal colonisation by candida, and hence contamination of specimens, makes it difficult to distinguish local from systemic infections, with the result that diagnosis may be delayed and appropriate treatment started late.

Between July 1981 and June 1984, 10 neonates and infants with systemic candidiasis were treated in the regional neonatal intensive care unit at this hospital. These babies are reviewed and the present scheme of management is described.

Patients, methods, and results

Patients. Details of the 10 babies are summarised in

Table 1 *Details of affected infants*

Case no	*Gestation (weeks)*	*Birthweight (g)*	*Admission diagnoses*	*Duration respiratory support (days)*	*Duration of IVH (days)*	*Central cannulation (days)*
1	28	1240	Preterm, hyaline membrane disease	1–24	5–24	Attempt failed
2	38	2920	Transposition of great vessels, subacute intestinal obstruction, thrombocytopaenia	15–20	30–35	Cardiac catheterisation 2 and 13. Long line
3	26	800	Preterm, hyaline membrane disease, post haemorrhagic hydrocephalus, ventriculoperitoneal shunts × 2	1–67	0–63	UAC 1–5
4	26	450	Extreme prematurity, elective ventilation	1–35	7–24	UAC 1–5
5	25	640	Extreme prematurity, recurrent apnoea	4–24	8–34	UAC 1–8 UVC 5
6	27	1000	Preterm, hyaline membrane disease, severe bruising	1–30	4–33	UAC 1–2
7	37	2640	Severe hyaline membrane disease, transitional circulation	1–25	5–34	UAC 1–7
8	26	730	Preterm, recurrent apnoea	4–10 13–25	8–31	UVC 1–4
9	26	700	Extreme prematurity, elective ventilation	1–15 21–32	5–41	UAC failed UVC 1
10	25	900	Extreme prematurity, elective ventilation	1–27	8–21	None

UAC=umbilical artery catheter; UVC=umbilical vein catheter; IVH=intraventricular haemorrhage.

Table 1. Eight were extremely preterm, with gestational ages between 25 and 28 weeks and birthweights between 450 and 1240 g.

Ventilation. All infants required early ventilation for inadequate respiratory effort, hyaline membrane disease, or both. No babies were permanently weaned from the ventilator before the age of 3 weeks, and one baby needed respiratory support for 67 days.

Central cannulation. Seven infants had umbilical arterial or venous catheters inserted on day one and left in situ for up to seven days. A further baby (case 2) underwent cardiac catheterisation twice via the femoral veins, and also had a central venous line inserted for total parenteral nutrition. All the other babies received total parenteral nutrition for up to 54 days via peripheral veins.

Antibiotics. Repeated courses of broad spectrum antibiotics had been given to all infants for suspected systemic bacterial infections. Seven of the 10 had positive blood cultures on at least one occasion, the organisms being *Staphylococcus albus, Clostridia* sp, *Serratia* sp, *Staph aureus, Actinobacter* sp, *Streptococcus viridans,* and *Strep faecalis.* Initial treatment was usually penicillin and an aminoglycoside (gentamicin or netilmicin) although cefuroxime, cloxacillin, ampicillin, amikacin, and metronidazole were used when clinically indicated.

Diagnosis. Table 2 shows the ages at screening and subsequent confirmation of infection with candida. In four, candida organisms were isolated from pharyngeal secretions or superficial sites up to 15 days before systemic infection was confirmed. Diagnosis was based on the presence of budding yeasts in urine obtained by suprapubic aspiration and in five babies this provided a diagnosis within 24 hours. After incubation periods of 4 to 11 days candida was isolated from peripheral venous blood in only four

Table 2 *Presentation of candidiasis*

Case no	*Sample*	*Day of sampling*	*Day yeasts reported*	*Organism*	*Day treatment commenced*
1	ET secretions	15	16	*Candida albicans*	22
	ET tube tip	19	21		
	Arterial blood	20	22		
	Urine	20	22		
2	Long line tip	49	51	*C albicans*	51
	Long line site	49	51		
	Venous blood	49	58		
	SPA urine	51	57		
3	SPA urine	228	229	*C albicans*	229
	CSF	233	235	*C parapsilosis*	
4	Eye swab	25	29	*C parapsilosis*	35
	Bag urine	29	30	*C albicans*	
	SPA urine	35	35	*C albicans*	
5	Tip of UAC	9	20	*C parapsilosis*	20
	ET tube	9	20		
	Pharyngeal secretions	9	20		
	SPA urine	10	20		
6	Venous blood	12	16	*C albicans*	16
	SPA urine	12	16		
	Pus from abscess	20	20		
7	ET secretions	12	15	*C albicans*	30
	Swab from IVI site	15	17		
	SPA urine	29	30		
8	Venous blood	13	23	*C albicans*	23
	Pharyngeal secretions	14	17		
	SPA urine	23	30		
9	SPA urine	31	31	*C parapsilosis*	31
	Arterial blood	31	26		
10	Venous blood	22	33	*C albicans*	41
	SPA urine	41	41		
	Throat swab	41	42		

SPA=suprapubic urine; ET=endotracheal; CSF=cerebrospinal fluid; IVI=intravenous infusion.

Table 3 *Treatment regimen and serum 5-flucytosine (5 FC) concentrations.*

Case no	*Drug(s)*	*Route*	*Dose (mg/kg/day)*	*Pre-dose (μg/ml)*	*Serum values 1 hour post dose (μg/ml)*	*Day of treatment*	*Total length of treatment (days)*	*Adverse effects*
1	5FC	IV/O	130	41	49	3	14	Anaemia. Transfused twice during treatment
2	5FC	IV	200	104	109	3	14	None
	5FC	IV	130	—	—	—		
	Amphotericin	IV	1·0	—	—	—	14	
3	5FC	O	180	44	64	6	16	None
4	5FC	O	150	44	47	3	12	Thrombocytopaenia after 9 days treatment responding to reduction in dose
			150	61	72	9		
			120	—				
5	5FC	IV	150	—			5	None
6	5FC	IV	120	34	62	5	18	Thrombocytopaenia. Both drugs discontinued for 5 days, restarted at same doses
	Amphotericin	IV	0·5	—	—	—	16	
7	5FC	IV/O	215	—	—	—	14	None
8	5FC	IV	200	60	90	3	9	None
9	5FC	IV	140	25	50	5	12	None
		IV	170	40	57	8		
10	1st course 5FC	IV	100	—	—	—	10	Relapsing infection and treatment failure
	2nd course 5FC	IV	100	—	—	—	18	
	3rd course 5FC	IV	100	26	39	5	5	
	Amphotericin	IV	0·5	—	—	—	23	

babies, while peripheral arterial blood cultures were positive in a further two babies with negative venous cultures.

The age at diagnosis of systemic candidiasis ranged from 12 to 226 days, the organisms being *Candida albicans* in seven babies and *Candida parapsilosis* in the remaining three. Both species were isolated from two babies; in case 4, isolation of *C parapsilosis* from an eye swab prompted further screening which isolated *C albicans*; in case 3, *C parapsilosis* was isolated from cerebrospinal fluid obtained during operative removal of a ventriculoperitoneal shunt after *C albicans* had been identified in suprapubic urine and treatment begun.

Treatment. Table 3 shows the drug and dosage regimens used, with the duration of treatment, adverse effects, and available drug concentrations. The initial treatment in all babies was 5-flucytosine, although in cases 2 and 6, amphotericin B was added within 48 hours when it became apparent that there was particularly widespread dissemination. Case 10 was well at the time the blood culture was undertaken, hence no treatment was started until clinical deterioration prompted a further infection screen. He failed to maintain a response to three separate courses of 5-flucytosine and by this stage a hard mass was palpable in his left flank. As the organism had become resistant to 5-flucytosine, amphotericin B was substituted, but without initial benefit. Laparotomy showed a large, pale, left kidney which was resected, allowing complete eradication of infection. Histology showed numerous small abscesses containing hyphae and yeast like bodies.

Initial doses of 5-flucytosine were 100 to 200 mg/kg/day. Blood concentrations were normally measured on the third day of treatment and both oral and intravenous routes produced peak values at the upper end of the therapeutic range of 50 to 100 mg/l. Because of the possibility of candida meningitis in case 4, drug concentrations were measured in cerebrospinal fluid from ventricular taps and were 20 to 67 mg/l. Amphotericin B was given as a single daily infusion and blood urea, electrolytes, and platelet count were monitored for signs of toxicity. The starting dose of 0·25 mg/kg was increased daily, if tolerated, to a maximum of 1 mg/kg/day.

Treatment was monitored by microscopy of serial suprapubic urine specimens and was stopped when three consecutive samples showed absence of hyphae and no growth on culture. Duration of treatment was 5 to 18 days in cases 1 to 9.

Possible toxic effects were seen in three babies with anaemia or transient thrombocytopaenia which was managed by dose reduction or temporary cessation of treatment. Interestingly, case 2 was thrombocytopaenic at diagnosis and her platelet count rose steadily during treatment.

Outcome. Two babies died during their first hospital admission and two died subsequently. No deaths were attributable to candidiasis or its treatment and there have been no recurrences in the survivors, nor any evidence of impaired immunity which would predispose to infection with yeasts.

Discussion

Babies at particular risk of systemic candidiasis are characteristically extremely preterm (28 weeks' gestation, or less) and have received long term ventilation, repeated courses of antibiotics, and total parenteral nutrition, though not necessarily via a central line.[2-4] Confirmation of systemic candidiasis is difficult, with several previous reports drawing attention to negative blood and cerebrospinal fluid cultures before the discovery of disseminated disease at surgery or necropsy.[2 3 6 12] Since candida has a predeliction for the urinary tract, it is essential that suprapubic urine should be examined in any baby suspected of fungal infection. We feel that the presence in urine of budding yeasts or hyphae is strongly suggestive of systemic infection and antifungal treatment should be started promptly pending the results of urine and blood cultures. Venous blood cultures may at times be misleading[5] and in two of our patients were negative while arterial blood cultures were positive. Subsequent confirmation of a fungal infection from blood may take several days (up to 11 days in this series), and clearly, appropriate treatment should be started as soon as possible. Usually urine microscopy and subsequent culture results give a more prompt diagnosis and should always be undertaken. Total and differential leucocyte counts show no consistent changes in the presence of systemic candidiasis. Symptoms of systemic fungal infection are nonspecific, the presenting feature often being simply a poor colour or lethargy. Other infants, however, may present with a fulminating illness indistinguishable from bacterial septicaemia. Previous isolation of candida from superficial sites or endotracheal secretions should raise the level of suspicion and ensure that a search for evidence of systemic candidiasis is included in the infection screen of these infants.

Broad spectrum antibiotic usage probably predisposes to the development of systemic candidiasis. In our series, however, five babies were being treated for culture positive bacterial septicaemia at the time candidiasis was diagnosed and in contrast to previously published recommendations,[5 12] there was no evidence that continuing antibiotics adversely affected the response to antifungal agents or subsequent outcome. Treatment remains the subject of discussion and debate, with miconazole,[2 6] ketoconazole,[7] 5-flucytosine, and amphotericin B[4 8 9 12] each having their advocates. While 5-flucytosine is known to cause bone marrow depression and to induce resistance after prolonged use, it has the advantages of excretion via the urinary tract and good absorption when given orally. Our experience suggests that 5-flucytosine alone is appropriate treatment for many babies who do not have a fulminating illness and in whom the diagnosis is made before multiorgan involvement has occurred. Amphotericin B is not absorbed from the gut and has poor penetration into body fluids when given parenterally. Although adverse effects in older children and adults include nephrotoxicity, hypotension, hypokalaemia, and thrombocytopaenia, amphotericin B was well tolerated and proved to be safe when used by gradually increasing the dose to 1 mg/kg/day. There is evidence that 5-flucytosine and amphotericin B act synergistically, both in vitro[10] and in the mouse.[11] The duration of treatment needed to eradicate systemic candidiasis is unknown[12] and often arbitrary. It is probably wise to use 10 to 14 days treatment initially (though shorter courses may be successful). Several negative urine cultures confirm erradication, though this may on occasions be temporary. Even in the absence of obvious symptoms, urine should be cultured periodically thereafter for several weeks.

Prevention of candidiasis in susceptible babies is difficult, but we are attempting to reduce the degree of colonisation by applying povidone-iodine ointment to puncture sites of intravenous cannulae and also by using twice daily oral nystatin painted inside the mouth.

The trend towards aggressive treatment of extremely low birthweight babies has led to an increase in the incidence of systemic candidiasis. Positive urine cultures suggest systemic disease and should prompt arterial (not venous) blood cultures followed by antifungal treatment. Bacterial sepsis may coexist and, therefore, antibacterial treatment should not be withheld. Our experience shows that where fungal infection is recognised early, safe and effective treatment can readily be achieved.

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