Pulmonary vascular candidiasis and use of central venous catheters in neonates

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SUMMARY A retrospective study of infant deaths in this maternity hospital carried out from 1976-86 showed a recent increase in fatalities with systemic candidiasis. Ten of twenty five cases occurred between July 1985 and June 1986. Most of these infants had *Candida* plugging pulmonary vessels, often accompanied by vasculitis, thrombosis, and parenteral lipid embolism. The adoption of central venous catheters for prolonged parenteral feeding of very preterm infants may have accounted for this phenomenon. Over the same decade there was an increased incidence of *Candida* isolates from all admissions to the neonatal intensive care unit: the prolonged survival of very low birthweight infants and the use of multiple courses of antibiotics were also factors.

Systemic candidiasis is a recognised and serious complication of neonatal intensive care and is associated with a high mortality.^{1 2} It occurs particularly in very low birthweight infants who have received multiple courses of broad spectrum antibiotics and who are fed parenterally.²⁻⁴ Over the past 12 months we have been aware of an increase in the number of infant deaths with systemic candidiasis in our neonatal intensive care unit. Most of these infants had central venous catheters, and showed *Candida* within the pulmonary vessels and a pulmonary vasculitis, an association which has been described previously.⁵ The aim of this study was to review our experience of the pathology of this condition over 10 years.

Material and methods

Necropsy records of babies dying in the neonatal medical and surgical units at this hospital between January 1976 and June 1986 were reviewed for cases of systemic candidiasis. All necropsies included histological examination of haematoxylin and eosin stained sections of all major organs and tissues, together with periodic acid Schiff stained sections where indicated, and microbiological culture of lung, and, in many cases, blood and cerebrospinal fluid. Systemic candidiasis was diagnosed when *Candida* pseudohyphae or yeast forms were seen histologically within tissues or blood vessels, or where positive

blood or cerebrospinal fluid cultures were obtained. A case in which permission for post mortem examination was refused but which was known to have systemic candidiasis on the basis of positive blood culture before death was also included.

Candidal isolates from the medical neonatal intensive care unit (NICU) were also reviewed during this period. Before 1981 the base for routine culture was nutrient broth (Oxoid) and agar (Oxoid) with 5% horse blood. Subsequently, Columbia blood agar base (Oxoid) was used, together with cultures on Sabouraud's dextrose agar (Oxoid) at 37°C for 48 hours. Since November 1979 it has been the policy to take rectal swabs routinely from all infants on the NICU.

Results

An increase in the number of candidal isolates from the NICU in the past 10 years occurred (fig 1), beginning in 1981: it was probably due in part to changes in culture policy with routine plating out on Sabouraud's medium. Over the same time period, however, there was a decline in the numbers of infants aged less than a week coming to necropsy, reflecting the longer survival of extremely premature infants as a result of intensive care. The commonest sites of isolation (table 1) were rectum, skin, urine, and umbilicus.

Between January 1976 and June 1986 25 infants died with evidence of systemic candidiasis (tables 2 and 3). Nearly all were of very low gestation (mean 27.2 weeks) and birthweight (mean 1028 g) and had

Fig 1 Percentage of admissions to neonatal intensive care unit with candidal isolates, 1976-85.

the complications associated with extreme prematurity. Most of the infants were cared for in the NICU, although a few (cases 5, 10, and 14) were treated in the neonatal surgical unit, and one (case 23) in the children's ward. Only eight of the infants were born in St Mary's Hospital, most being transferred from other hospitals within hours or days of birth. Most of the babies received multiple courses of antibiotics, and in some cases as many as seven different antibiotics were given before the onset of systemic candidiasis. All of the babies received intravenous fluids, and those who survived in excess of 14 days were fed parenterally. Most had umbilical arterial catheters, and 16 had indwelling central venous catheters usually inserted into the jugular vein. Although a few of the babies died in the second week of life, most lived longer (mean survival 37.2 days).

Table 1 *Candida* isolates from neonatal intensive care unit 1976-85

Site	No	%	Site	No	%
Rectum	265	(32.7)	Catheter tip	18	(2.2)
Skin	85	(10.5)	Gastric	17	(2.1)
Urine	76	(9.4)	Wound	17	(2.1)
Umbilicus	61	(7.5)	Urine (SPA)	8	(1.0)
Throat	60	(7.4)	Ear	8	(1.0)
Buttocks	47	(5.8)	Eye	6	(0.7)
ETT	44	(5.4)	CSF	3	(0.4)
Nose	34	(4.2)	Vagina	3	(0.4)
Mouth	33	(4.1)	Others	5	(0.6)
Blood	20	(2.5)			

Total No of isolates 811

ETT: Endotracheal tube.

Although *Candida* was isolated from superficial sites during life in most cases, in only five were positive blood cultures obtained (table 3). The organism was grown from cerebrospinal fluid in two cases and from urine in nine. At post mortem the organism was seen most commonly within the lungs (18 cases), followed by heart (n = 7), kidney (n = 7), peritoneum (n = 6), brain (n = 6), and adrenal (4).

Pathologically the cases could be divided into four broad groups based on the site of infection (table 4).

PULMONARY VASCULAR

Candidal yeasts and occasionally pseudohyphae were present within medium and small pulmonary vessels (figs 2 and 3), often accompanied by recent or organising thrombus, inflammatory debris, and lipid material with the appearance of parenteral lipid (Intralipid, KabiVitrum) (fig 4). In many cases there was a necrotising pulmonary vasculitis (fig 5), although this appearance was sometimes seen in vessels which did not contain *Candida*, in addition to those which did. In this group organisms were not often seen within the airways and alveoli. In most cases, however, dissemination of yeasts, and, on occasion, pseudohyphae to other parts of the body had occurred. All 12 infants with pulmonary vascular candidiasis had central venous catheters, and of the 16 infants with a catheter, only three did not show this histological appearance. (Post mortem examination was not performed in the remaining case.)

Table 2 Clinical data

No	Gestation (weeks)	Birth weight (g)	Survival (days)	Diagnosis	No of antibiotics	Umbilical arterial catheter	Central venous catheter
1	32	1000	60	IRDS	4	+	+
2	29	1230	28	IRDS, pneumonia, jaundice	5	?	?
3	26	695	13	IVH, pneumonia	3	?	?
4	30	1140	35	IVH, pneumonia	5	+	?
5	30	1400	64	Ileal atresia, NEC	6	—	+
6	26	860	9	Birth asphyxia, IVH, jaundice	3	+	—
7	27	1000	14	Birth asphyxia, pneumonia	4	+	—
8	25	940	35	Pneumonia, jaundice	5	+	+
9	26	980	56	Asphyxia, jaundice, IVH hydrocephalus, CMV	6	+	—
10	26	960	25	NEC	3	+	—
11	27	950	32	IRDS, IVH, transposition	3	+	—
12	26	1000	31	Pneumonia, jaundice	5	+	+
13	26	790	34	IRDS, IVH, PVL	6	—	+
14	25	860	8	Jaundice, NEC, DIC	4	+	+
15	27	800	7	IRDS, IVH, renal failure	2	+	—
16	23	620	43	Birth asphyxia, jaundice, IVH	5	+	+
17	26	1000	33	Asphyxia, IRDS, IVH, gastric perforation	7	+	+
18	24	780	63	Ruptured oesophagus, IVH, PVL	6	+	+
19	25	750	14	Sepsis, jaundice, intestinal perforation	4	—	+
20	26	1130	31	IVH, pneumonia, jaundice	7	+	+
21	26	938	27	IRDS, jaundice, IVH	7	+	+
22	26	575	55	IRDS, sepsis, jaundice, IVH	4	+	+
23	40	2750	156	Congenital varicella	6	—	+
24	29	1500	23	Asphyxia, jaundice, IVH	7	+	+
25	28	1060	35	IRDS, pneumonia, BPD, IVH, PVL	7	+	+

BPD: Bronchopulmonary dysplasia; CMV: cytomegalovirus; DIC: disseminated intravascular coagulopathy; IRDS: idiopathic respiratory distress syndrome; IVH: intraventricular haemorrhage; NEC: necrotising enterocolitis; PVL: periventricular leucomalacia.

Table 3 Pathological data

Case No	Antemortem cultures	Post mortem cultures	Lungs	Histology of gastrointestinal tract	Others
1	Skin, umbilicus, stool, urine	CSF	—	—	Heart, kidney, brain
2	Trachea	Lung, blood, skin	Airways	+	
3	Throat, nose, umbilicus, rectum	Lung, blood, rectum	Airways	+	
4	Peritoneal fluid	Peritoneum	—	+	Peritoneum
5	Skin	Lung, peritoneum	—	+	Peritoneum
6	Ear, nose, throat	Lung, blood	Airways	+	
7	Umbilicus, UAC, ETT	Lung, blood	Airways	+	Peritoneum
8	—	—	Vessels	—	Heart, kidney, brain
9	Umbilicus, urine, rectum	Lung, blood, urine	Airways	—	
10	—	Peritoneum	—	+	Peritoneum
11	Umbilicus, urine, blood, rectum	Lung, blood, urine, pericardium	—	—	
12	Rectum, throat, ETT, urine, umbilicus, CSF	Lung, blood	Vessels	—	Heart, kidney, brain, marrow, liver, adrenal, thymus, thyroid
13	—	—	Vessels	—	Inferior vena cava
14	Stomach, peritoneum, ETT	Lung, blood	Airways	—	Peritoneum, bladder, spleen
15	Stomach, ETT, chest drain	Lung	—	+	Pleura
16	—	—	Vessels	—	Brain
17	Urine, buttocks	Blood	Vessels, airways	—	Heart, kidney, brain, spleen, adrenal
18	Blood, urine (SPA)	Blood	Vessels	+	Kidney
19	—	Lung, blood, CSF	Vessels	+	Heart, kidney, peritoneum, thyroid, pituitary, adrenal
20	Urine, blood, peritoneum	(No necropsy)			
21	Umbilicus	—	Vessels	—	Spleen
22	Rectum, blood, urine	Lung	Vessels	—	
23	Pharynx, buttocks	—	Vessels	—	
24	Urine, ETT, throat, blood, CSF	Lung, brain, liver, blood	Vessels, airways	+	Brain, kidney, heart, liver, aorta, adrenal, spleen, thyroid
25	—	—	Vessels	—	Heart

CSF: cerebrospinal fluid; ETT endotracheal tube; SPA: suprapubic aspirate; UAC: umbilical arterial catheter.

Table 4 Annual incidence of pulmonary vascular candidiasis, peritoneal candidiasis, respiratory tract candidiasis and other types of candidiasis in necropsies

	Year (July-June)										
	75-76	76-77	77-78	78-79	79-80	80-81	81-82	82-83	83-84	84-85	85-86
Total No of cases	1	0	2	1	1	4	1	2	2	1	10
Pulmonary vascular	—	—	—	—	—	1	—	1	1	—	9
Peritoneal	—	—	—	1	1	1	1	—	1	—	—
Airway	—	—	2	—	—	2	—	—	—	—	—
Other	1	—	—	—	—	—	—	1	—	1	1

Fig 2 Candidal yeasts occluding medium and small pulmonary vessels. (Periodic acid Schiff stain.)

Fig 3 Candidal organisms, predominantly yeast forms, occluding pulmonary vessel, with early invasion of wall. (Periodic acid Schiff stain.)

Fig 4 *Candida* and lipid droplets occluding small pulmonary artery. (Periodic acid Schiff stain.)

PERITONEAL

This group was characterised by *Candida* peritonitis following intestinal perforation. *Candida* pseudohyphae were seen in the peritoneum, within the intestinal lumen, and often in the bronchi and bronchioles. Occasionally organisms were disseminated elsewhere.

AIRWAY

Histological evidence of the organism was confined to the gastrointestinal tract and airways, including bronchioles. Although post mortem blood cultures were positive, no invasion of the tissues by *Candida* was seen.

Fig 5 *Candida* within small pulmonary vessel with vasculitic changes. (Periodic acid Schiff stain.)

OTHER

A few cases did not fit into any of the above three groups, either because no post mortem examination was performed, because *Candida* was not seen histologically despite positive blood cultures, or because a different pattern of infection was seen.

Table 4 shows the incidence of systemic candidiasis at necropsy over the study period: a noticeable increase in incidence in the 12 months from July 1985 to June 1986 occurred, and this increase comprised only cases with *Candida* within pulmonary vessels. In contrast, the other groups showed no recent rise in incidence.

A variety of histological appearances was seen in other organs. In the kidney *Candida* was seen most commonly within renal tubules, particularly in the medulla, with abscess formation and destruction of renal tissue in some cases. In one infant yeasts were present in afferent arterioles and glomerular capillaries, accompanied by focal necrosis of the glomerular tufts. Appearances in the brain ranged from yeasts within small cerebral and meningeal vessels to massive infiltration of cerebrum, cerebellum, and brain stem by pseudohyphae. Organisms were commonly seen in the periventricular region. In one case there was a striking granulomatous response, especially in the cerebellum with organisms present within giant cells. Cardiac disease included endocarditis with valvular vegetations, yeasts within small myocardial vessels, and myocarditis with necrosis.

Discussion

There has been a striking increase in the number of cases of systemic candidiasis at necropsy at this hospital in the 12 months from July 1985 to June 1986. In nearly all of these cases the organism was seen within pulmonary vessels, often with thrombus, inflammatory exudate, and intralipid, although in many of these infants there was no histological evidence of candidal colonisation of either the airways or gastrointestinal tract. The rise in incidence of systemic candidiasis coincided with an increased use of central venous feeding lines on the unit. It seems that a common portal of entry in these infants was via an indwelling central venous catheter inserted to facilitate parenteral nutrition. Most infants with systemic candidiasis also had umbilical arterial catheters. Although there is no doubt that these are occasionally colonised by *Candida* with consequent systemic distribution of the yeast, the recent rise in fatal candidiasis has been in infants in which *Candida* predominated in the pulmonary vessels (table 4), where systemic venous rather than arterial contamination is a more likely explanation. Moreover, the few necropsies with pulmonary vascular candidiasis, which occurred

before the routine adoption of long central venous catheters in July 1985, were also cases in which such a venous catheter had been used. Umbilical arterial catheters, on the other hand, have been used in most seriously ill infants on the intensive care unit to monitor blood gases for many years prior to July 1985, when the increase in fatal systemic candidiasis was seen.

The different patterns of pulmonary disease have been noted by other workers. Kassner *et al* found that the commonest pattern of pulmonary candidiasis in infants was the embolic type, in which thrombi containing large numbers of *Candida* spores and pseudohyphae were present in pulmonary arteries with multiple haemorrhagic infarcts.⁶ The portal of entry in these was considered to have been venous catheters. Less commonly, bronchopulmonary (air space invasive) and disseminated (capillary invasive) forms were seen. Rose *et al*, in a study of adults with pulmonary candidiasis, found a necrotising vasculitis affecting pulmonary vessels in five of six patients in whom the portal of entry had been a venous catheter.⁵

Systemic candidiasis is known to complicate the use of indwelling vascular catheters for parenteral nutrition.⁷⁻⁹ The risk of infection increases with the length of time the catheter has been in situ.^{8,9} The organisms can enter the body along the side of the catheter, and the tip provides a nidus for colonisation and subsequent embolisation of *Candida*. Parenteral feeding solutions can support the growth of yeasts,¹⁰ although this was never shown in the present series. Broad spectrum antibiotic treatment also predisposes to *Candida* sepsis. Indeed, chemotherapy is the commonest potential predisposing factor to serious disseminated candidiasis in patients of all ages.^{8,11} All of the patients in our series had received multiple courses of parenteral broad spectrum antibiotics, and in some cases as many as seven different antibiotics had been given over a period of only a few weeks (table 2).

The rise in fatalities from systemic candidiasis in the NICU was preceded by a pronounced increase in the number of isolates among all admissions to the unit (fig 1). Although this increase may be explained in part by the introduction of routine rectal swabbing of all NICU infants in 1979, and of the routine use of Sabouraud's medium in 1981, there have also been considerable changes in the population of the unit over the past decade, with a large rise in the proportion of very low birth weight infants who are particularly susceptible to colonisation by *Candida*.¹² More of these very tiny babies are surviving the first week of life, thus increasing the likelihood of colonisation. The immature immune system in these sick preterm infants may be less capable of dealing with the

organism than the relatively more mature infants who populated the unit before 1981.

The nature of the work of a neonatal intensive care unit is such that it is difficult to see how candidal colonisation, antibiotics, and catheterisation can be avoided. Our enquiries, however, suggest that long central intravenous lines via the jugular vein pose a particular risk.

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