Candida strains from neonates in a special care baby unit

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Abstract

Carriage and acquisition of *Candida* spp and *Candida albicans* biotypes were studied among 163 neonates and 90 staff in a neonatal intensive care and surgical unit during a 17 week period. Twenty one neonates carried yeasts in the mouth, rectum or groin when first sampled, and a further 25 were positive later. *C. albicans* accounted for 94.7% of 431 yeast isolates from neonates but only 67.4% of 43 isolates from staff. The first isolated *C. albicans* biotype persisted in 13 babies monitored longitudinally. Simultaneous colonisation with two *Candida* spp was found in 2/46 neonates and 5/33 staff. The prevalence of candida was significantly higher among babies of gestational age <28 weeks (65%) than those of higher gestational age (26%). Oral and/or crural candida infection was observed in 14 of the babies but none developed deep seated candidosis. Routine antifungal prophylaxis did not affect the frequency of yeasts among the neonates.

Deep seated forms of candida infection occur relatively infrequently in neonatal special care units¹⁻⁴ but at least one cluster of cases of disseminated candidosis has been reported in this setting⁵ and an overall incidence as high as 3-4% has been estimated by some investigators.⁶⁻⁷ Carriage of candida is common in neonatal units; oral and cutaneous candidosis may arise frequently and stringent antifungal antisepsis can markedly reduce the prevalence of the fungus and the incidence of candida pathologies among special care neonates.⁸⁻¹¹

In most of the studies cited it has been presumed that neonatal candida infection in special care units results usually from cross infection. Phelps *et al* confirmed the occurrence of candida cross infection during an outbreak of superficial candidosis in a neonatal unit by demonstrating that a similar range of *Candida albicans* biotypes was isolated from staff and from affected babies.¹² Cross infection by *C. albicans* has also been demonstrated in adult intensive care units.¹³⁻¹⁵

Estimates of candida carriage among neonates in special care facilities vary considerably. Phelps *et al*¹² found an overall candida colonisation rate of only 10% among 29 neonates, while higher prevalences of 19% and 27% were reported, respectively, by Hageman *et al*,¹⁶ and Baley *et al*.¹⁷ Lay and Russell showed that recoveries of yeasts from oral swabs increased with the duration of a baby's stay in a special care unit: 53% of the babies who had stayed for

14 days in the unit they surveyed carried yeasts.¹¹

The survey by Phelps *et al* is the only one so far to involve strain typing of *C. albicans* isolates as an epidemiological marker; however, this study did not involve systematic prospective sampling of the neonates and only strains from babies with pathological candidosis were typed.¹² The present study was undertaken to examine candida carriage in a prospective survey of unselected neonates in a special care unit who were sampled repeatedly during their stay on the unit. Staff in the unit were also sampled for candida carriage, and *C. albicans* isolates were biotyped to determine whether the spectrum of phenotypic types in the neonates differed from that in the staff.

Patients and methods

The survey involved all 163 neonates and 90 staff present in the regional neonatal intensive care and surgical unit at Leeds General Infirmary during May to September, 1986, and a further 13 neonates selected for their extreme prematurity and sampled during the following year. The unit could accommodate a maximum of 36 babies at one time. It was divided into two sections—the special care (including intensive care) and the surgical areas. An 'open door' visiting policy existed for members of the neonate's immediate family, but other visitors were actively discouraged from attending.

The neonates in the main survey comprised 77 who were under 37 weeks' gestational age or diagnosed as suffering from respiratory distress syndrome ('premature' group), 39 admitted for surgical correction of oesophageal atresia, imperforate anus, hiatus hernia, congenital heart defects, gastroschisis, or biliary atresia ('surgical' group), and 47 with miscellaneous diagnoses, including infection, repeated cyanotic attacks, persistent jaundice, meconium aspiration, Down's syndrome, hydrops, repeated vomiting, etc ('others' group).

Anti-infection care of the neonates involved applications of an oral antiseptic solution swabbed around the inside of the mouth three to four times daily. All babies receiving antibiotic therapy also routinely received antifungal prophylaxis with miconazole gel or nystatin solution three times daily.

In the main survey, the sampling was done in two phases of eight weeks, separated by one week during which all staff who came into contact with infants were sampled. Because of the high turnover of staff and their constant movement through all areas of the unit it was

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Accepted 25 July 1991

not possible to monitor the positions of staff during the periods in which babies were sampled. For isolation of yeasts from the babies, sterile swabs premoistened in sterile 0.15 M saline were used to sample the mouth, rectal, and crural areas. These samples were taken twice a week four to five hours after the babies had received their routine drug treatments and antisepsis. Swabs were smeared on the surface of plates of Sabouraud's glucose agar (Oxoid) which were incubated for 48 hours at 37°C. Staff were sampled with oral swabs and by fingerprint impressions on Sabouraud's agar. The latter were made after staff had thoroughly washed their hands in Hibiscrub (4% chlorhexidine chlorate; ICI), as hand washing with this agent before and after handling babies was a routine procedure on the unit. The atmosphere of the unit was sampled once during each phase of the study with a Reuter Centrifugal Air Sampler, and the sterilising fluid, thermometers, zinc oxide skin cream, and 20 samples of aspirated breast milk used in the unit were also cultured for yeasts.

All samples that yielded yeast colonies were processed further for identification of the species isolated. Isolates that gave unequivocal positive results in the germ tube test for *C. albicans* were identified as *C. albicans*. Equivocal and negative germ tube isolates were further identified to the species level by means of API 20C AUX strips (API System, SA) and with traditional fermentation and assimilation tests¹⁸ when necessary. Three quarters of the *C. albicans* isolates from the babies and all of the isolates from staff were biotyped by the procedure described by Odds and Abbott.^{19, 20} This procedure involves tests for the growth of each isolate on nine agar media that detect their ability to grow at pH 1.4, production of zones of proteolysis, resistance to flucytosine, boric acid and safranin, salt tolerance, and utilisation of urea, sorbose, and citrate. Individual biotype patterns were referred to by means of three digit codes in which each digit uniquely encodes the results of three of the nine tests where a positive result is scored 1, 2, or 4, and the digit represents the total score for these tests. For example, a result of ++--+-+ would be encoded as 364. When multiple isolates were obtained from the same site in a patient on different occasions, a consensus biotype profile was determined by an algorithm described previously.²¹ This procedure guarded against overinterpretation of differences in biotype test results as indicating strain variation: only biotypes that varied from the consensus type in more than two tests were considered as a different strain of *C. albicans*.

Statistical analyses of the data were performed where appropriate by the χ^2 test or by Student's *t* test.

Results

YEAST PREVALENCE AMONG NEONATES

A total of 2386 samples were taken from 163 neonates during the main survey period. Of these, 431 (18.1%) yielded yeasts on culture; they came from 46 (28.2%) of the neonates.

Twenty three (27.7%) of the 83 boys and 23 (28.8%) of the 80 girls were yeast positive (difference not significant). The carriage of yeasts among babies in the different admission categories was also statistically the same: 19/77 (24.7%) 'premature' babies, 13/39 (33.3%) 'surgical' babies, and 14/47 (29.8%) 'other' babies were yeast positive. Of the 46 yeast positive neonates, 21 were positive at the time of the first sample, and were therefore either yeast carriers at the time of their admission or may have acquired the organism on the unit before being sampled, and 25 became yeast positive in later samples and were presumed to have become yeast carriers during their stay on the unit. Crural (or perianal) pathologies and oral pathologies compatible with a candida infection were seen in 12 and two babies, respectively, during the survey (all these cases gave positive cultures). There were no instances of deep seated candida infection.

Four neonates each were colonised with *Candida* spp in oral or crural sites only and nine neonates were yeast positive only in rectal samples. Five neonates were colonised both orally and rectally but not crurally; 13 gave simultaneous positive crural and rectal cultures but remained yeast negative in oral samples, and 13 carried yeasts in all three sites sampled. No examples of oral plus crural colonisation with negative rectal cultures were found.

Only seven neonates with low birth weight (500–1000 g) and seven with a gestational age of 28 weeks or less were sampled during the main survey. Of these, four (57.1%) and five (71.4%), respectively, were positive for yeasts, as compared with 42/156 (26.9%) and 41/156 (26.3%) of babies with higher birth weights or gestational ages. Because these differences in yeast positivity approached statistical significance but the groups of extremely premature neonates was so small, an additional 13 babies with gestational age of 28 weeks or less were selected and sampled once subsequent to the main survey. Of these additional 13, eight (61.5%) carried yeast in one or two sites. Thus, the overall carriage rate of yeasts in neonates of very low gestational age (13/20; 65.0%) was significantly higher than the rate in neonates of higher gestational age (41/156; 26.3%)— $p < 0.001$.

Routine antifungal prophylaxis appeared to have no significant influence on yeast carriage. There were 15 yeast positive neonates among the 52 who received miconazole (28.8%), 14 among the 42 who received nystatin (33.3%), and 17 among the 69 who received no prophylaxis (24.6%)—differences were not significant. Duration of stay in the neonatal unit also bore no significant association with yeast carriage: the mean (SD) duration of stay for babies who yielded at least one yeast positive sample was 25.5 (38.5) days as compared with 18.5 (15.7) days for babies who stayed yeast negative throughout.

SPECIES AND BIOTYPES OF YEASTS ISOLATED FROM NEONATES

C. albicans was the species most frequently isolated among the neonates. It accounted for

408 (94.7%) of the 431 cultures obtained during the main survey. *C. famata* was isolated once (0.2%), *C. glabrata* four times (0.9%), and *C. parapsilosis* 18 times (4.2%). All but two of the 46 yeast positive neonates were colonised with a single species—*C. albicans* in 37 (80.4%), *C. parapsilosis* in six (13.0%), and *C. famata* in one. Two babies yielded samples that contained both *C. albicans* and *C. glabrata* in the same cultures—twice from the rectal swab in one and twice from the crural swab in the second.

A total of 306 *C. albicans* isolates from 37 neonates was biotyped. The biotypes isolated are summarised in table 1. The prevalence of different biotypes was very similar for the three sites sampled: this observation, together with the longitudinal data (see below), suggests that most individual neonates acquired the same *C. albicans* strain in different anatomical sites while they were in the unit. Biotype 157 was the most commonly isolated type of the 22 different types found: flucytosine resistant biotypes (first digit of the code is 4 or more) accounted for 18%, 22%, and 25% of isolates from the rectum, groin, and mouth respectively (differences not significant).

In 13 instances a total of 6–38 separate *C. albicans* isolates was obtained from the same patient, permitting longitudinal monitoring of the *C. albicans* types carried by the neonates

(table 2). Unequivocal examples of more than one biotype occurring in the same patient were found for only 3/37 neonates (8.1%) and different biotypes were detected in a single specimen on only two occasions. Each neonate carrying yeasts in two or three of the sites sampled harboured the same biotype in the different sites. The persistence of a given strain type in an individual neonate was sometimes impressive, exceeding 30 days in seven of the 13 neonates summarised in table 2 and exceeding 60 days in three. There were no examples of babies whose *C. albicans* biotype or other yeast species altered to a different one with time, as has been reported for some adult patients with haematological malignancies.²¹

YEAST PREVALENCE AMONG STAFF

A total of 270 samples was taken from 90 staff (seven medical personnel, 78 nursing staff, and five others). Forty three samples (15.9%) from 33 staff (36.6%) gave positive cultures for yeasts. Of the 33 yeast positive staff, 28 carried yeasts in the mouth, four carried yeasts in the mouth and on the fingers, and one carried yeasts on the fingers only. There was a greater diversity of yeast species found among the staff than among the neonates, a lower prevalence of *C. albicans* and a higher prevalence of samples containing more than one species. *C. albicans* was isolated from the mouths of 28 staff and once from the fingers of an oral carrier, *C. krusei* was isolated from two oral samples and four finger samples, *C. famata* was isolated once from the mouth and fingers, and *C. parapsilosis* was obtained three times from finger samples alone. *C. glabrata*, *C. guilliermondii*, and *Saccharomyces cerevisiae* were each isolated from single oral samples (the yeast species other than *C. albicans* were coisolated with *C. albicans* on three occasions). The overall prevalence of *C. albicans* was therefore 67.4%, as compared with 94.7% of isolates from the neonates. Five members of staff carried two yeast species and two of these also carried more than one *C. albicans* biotype.

The *C. albicans* biotypes carried by the staff also showed a greater diversity than was found among the neonates. Twenty three different types were determined from 33 staff (table 3) as compared with 22 different types from 46

Table 1 Number of occurrences of *C. albicans* biotypes among 37 yeast positive neonates in three anatomical sites

Biotype	Oral swabs	Crural swabs	Rectal swabs
033	1	1	1
071	0	1	0
073	1	1	1
153	1	0	0
157	2	6	6
1 5/7 7	1	1	1
171	0	0	1
211	1	1	1
2 1/5 1	1	1	1
253	1	1	1
333	0	2	2
353	1	1	1
357	0	1	1
371	1	0	1
377	1	1	3
451	0	1	1
467	1	0	0
512	0	1	0
532	1	0	1
551	1	0	1
557	1	2	2
757	0	0	1

Table 2 Longitudinal carriage of *C. albicans* biotypes among 13 neonates who yielded six or more yeast positive cultures

Patient No	Oral			Crural			Rectal		
	Biotype	No of isolates	Duration (days)	Biotype	No of isolates	Duration (days)	Biotype	No of isolates	Duration (days)
1	157	2	7	157	15	53	157	15	53
2	033	3	11	016	1		033	4	18
3	557	1		033	1		357	1	
4				357	2	18	557	2	21
5				557	6	21	451	4	21
6	2 1/5 1	5	21	451	4	25	400	2	21
7	157	1		<i>C. glabrata</i>	2	14	157	6	21
8				157	5	14	2 1/5 1	16	70
9				2 1/5 1	14	70	<i>C. glabrata</i>	2	46
10				157	3	10	157	3	10
11				333	6	14	333	6	14
12	532	10	63	1 5/7 7	14	56	1 5/7 7	14	56
13	073	8	38	071	9	49	071	9	49
				377	5	39	377	8	74
				512	14	63	532	14	63
				073	6	28	071	11	45

Table 3 Prevalence of *C. albicans* biotypes isolated from staff in the neonatal special care unit

No of times isolated	Biotypes
1	051, 075, 101, 121, 173, 253, 257, 271, 313, 333, 353, 355, 356, 457, 557, 651, 757
2	157, 251, 351, 357, 577
3	177

neonates. However, the strain types from the staff were all determined from single samples, so the apparent diversity of types may be exaggerated.²²⁻²³ All the biotypes cultured from the neonates, or closely related strains, were represented among the staff isolates. The prevalence of flucytosine resistant isolates among the staff isolates was 20.0%—essentially the same as among the neonatal isolates.

YEASTS RECOVERED FROM ENVIRONMENTAL SOURCES

All samples from the air, fomites, and other environmental sources in the special care unit were negative for yeasts in culture.

Discussion

The overall candida colonisation rate of 28.2% among special care neonates in this study agrees well with the rate of 27% found by Baley *et al.*¹⁷ It is higher than the 10% and 19% frequencies reported by Phelps *et al.*¹² and Hageman *et al.*¹⁶ In common with these authors we found a lower prevalence of yeast colonisation in oral samples than in samples from the groin or rectum: the overall prevalences were 13.5% (oral), 18.4% (crural), and 24.5% (rectal). We therefore agree with Phelps *et al.*¹² and Hageman *et al.*¹⁶ that the lower digestive tract appears to be the first site of yeast colonisation among most neonates in a special care unit and that yeasts are readily spread from the anal region to the groins. Surveys of healthy children and adults and of hospital outpatients have usually consistently shown higher prevalences of yeasts in oral than in faecal, anal, or rectal samples²³; we suggest that the abnormally low oral yeast prevalence in our study arises both from the frequent oral antisepsis used on the unit and the fact that most of the babies were fed via nasogastric tubes. Other surveys of neonates receiving special care have found higher prevalences of yeasts in the mouth than in samples from other sites¹²⁻²⁴ and Lay and Russell¹¹ isolated *Candida* spp or other yeasts from 53% of the mouths of babies who remained in a special care unit for 14 days.

The considerable variations between the different surveys strongly suggest that rates of candida carriage may be altered by the conditions that prevail in a special care unit; management protocols that may enhance or reduce transmission of candida, and the nature and intensity of routine anti-infective hygiene measures employed: as all the surveys used swabs as sampling devices the differences are unlikely to be attributable to methodological variations. The composition of the patient

populations in the different studies is also likely to influence the apparent carriage rates: for example, study populations with a high proportion of patients of low birth weight might be expected to have a higher candida prevalence, as we found a much higher rate of yeast colonisation among babies of very low gestational age. However, 75% of the babies studied by Baley *et al.*¹⁷ had birth weights <1500 g, yet their candida carriage rate was not higher than ours. Thus, differences between studies probably reflect complex differences between units and their protocols more than any simple single factor.

One factor that should, in theory, alter rates of candida carriage is the prophylactic use of antifungal drugs. However, in the present study neither miconazole gel nor nystatin suspension given orally significantly affected the candida carriage rates. The quantities of these drugs used (0.2 ml in each case) may have been too small to affect candida colonisation. Harris *et al.*, who reduced oral candida carriage among their neonates by 50% with nystatin, used five times this dosage.⁹

The *Candida* spp isolated from the neonates in our study were qualitatively very similar to those reported in similar settings by others. Hageman *et al.*¹⁶ found *C. parapsilosis* in 38% of the neonates they studied and *C. glabrata* in 4%. Baley *et al.*¹⁷ found *C. albicans* in 62%, *C. parapsilosis* in 18%, *C. tropicalis* in 8%, and *Trichosporon pullulans* in 3%. However, the overall prevalence of *C. albicans* in our study (95%) was much higher than in either of the others cited, and much higher than the 67% prevalence of *C. albicans* isolated from the staff (though this may be at least partly determined by the different sites sampled in the two groups). The particularly high prevalence of *C. albicans* in the neonates studied gives some cause for concern. In his extensive review of epidemiological publications on candidosis, Odds calculated that *C. albicans* accounted for 70% of oral yeast isolates, 51% of anorectal tract isolates, and it was rarely recovered from skin samples except in patients with cutaneous candida infections.²³ It seems likely that this most pathogenic of the *Candida* species was selected for in the neonatal population, placing them at heightened risk of candida based pathology.

The spectra of *C. albicans* biotypes found among staff and patients were broadly similar. Type 157 was previously associated with an outbreak of disseminated candidosis in a hospital intensive care unit¹³ and with disseminated candidosis in heroin addicts.²⁵ As it was also the most prevalent biotype among the neonates (table 1), our findings confirm that this particular biotype may have a higher ability than some other strains to colonise patients. The strain types 153 and 157/7 are closely related to type 157: considered together, these strains were involved in seven of the 12 instances of cutaneous (crural) candida associated pathology and one of the two instances of oral thrush diagnosed during this study. Coincidentally and anecdotally, two cases of disseminated candidosis that were diagnosed in our

unit before the present study was undertaken were both caused by *C. albicans* biotype 157.

Our study was done before the advent of methods suitable for DNA typing of *C. albicans*^{15 26 27} so that only phenotypic differentiation was done. It will be interesting in the future to determine whether DNA typing reveals similar associations between particular *C. albicans* genotypes and neonatal candida carriage and infection.

It was not possible to monitor possible routes of transmission of candida between individual staff and patients. Nor were we able to sample parental yeast flora for administrative and ethical reasons. However, the general similarities between the *C. albicans* biotypes isolated from staff in the unit and the absence of *C. albicans* in samples from the environment strongly implicate person to person contact as the major route of transmission of candida in the unit. The stability of *Candida* spp and biotypes isolated longitudinally from babies in the neonatal unit suggests that, even if the initial colonisation event amounts to cross infection, the colonising strain remains immune from subsequent replacement by other strains or species in the unit. This situation differs from that seen in a longitudinal study of candida carriage in patients with haematological malignancy, where changes in candida flora were found in oral and stool samples, particularly in patients monitored for longer than 14 days.²¹ We agree with Phelps *et al*¹² that transmission between staff and neonates is, in the circumstances, the most likely means for propagation and dissemination of potentially pathogenic yeasts within a neonatal special care unit.

We are grateful to the late Peter Congdon and to the staff of the Regional Neonatal Intensive Care and Surgical Unit, General Infirmary, Leeds, for their help and cooperation. This study was supported by grants from the Wellcome Trust and the Yorkshire Regional Health Authority.

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