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SHORT REPORT

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In a UK national surveillance study, we found that *Candida parapsilosis* accounted for one quarter of all cases of invasive fungal infection in very low birthweight infants. *C parapsilosis* was associated with fewer deep-seated infections than *C albicans*, but mortality was similar. Ongoing surveillance is needed to monitor the epidemiology of invasive fungal infection in very low birthweight infants.

Over the past decade, *Candida parapsilosis* has emerged as an important nosocomial pathogen in very low birthweight (VLBW; <1500 g) infants.[1] In animal models, *C parapsilosis* seems to be a less virulent pathogen than *C albicans*, as it is less able to adhere to and penetrate the endothelium.[2] However, a recent systematic review of 34 observational studies was unable to determine whether the clinical course of *C parapsilosis* infection is less severe (less end-organ involvement and mortality) than *C albicans* infection in VLBW infants.[1] Most of the studies cited in the review were single-centre retrospective studies that may have been subject to ascertainment or referral biases. The review identified the need for a large prospective population-based study to assess the relative severity of infection from these organisms in order to inform infection control and treatment strategies.

METHODS

We undertook a national prospective surveillance study of invasive fungal infection in VLBW infants in the UK between February 2003 and February 2004. We used the British Paediatric Surveillance Unit reporting system and reconciled reports with cases identified through routine laboratory reporting to the Health Protection Agency (England, Wales, Northern Ireland), the Scottish Centre for Infection and Environmental Health (Glasgow, Scotland), and the UK Mycology Reference Laboratory (Bristol, UK). The surveillance study methods and case definitions are described in detail elsewhere.[3] We compared the frequency of exposure to putative risk factors for invasive fungal infection and the clinical features and outcomes in infants with confirmed *C parapsilosis* versus *C albicans* infection. The Scottish Multi-centre Research Ethics Committee and the Health Protection Agency Ethics Committee approved the study.

RESULTS

We identified 94 cases of invasive fungal infection and estimated the overall incidence to be 10 (95% confidence interval (CI) 8.0 to 12.0) cases per 1000 VLBW live births. *Candida* species were isolated in 87 (93%) cases; 23 (24%) were identified as *C parapsilosis* (2.4 (95% CI 1.4 to 3.4) cases per 1000 VLBW live births) and 50 (53%) as *C albicans* (5.3 (95% CI 3.8 to 6.8) cases per 1000 VLBW live births).

Infants infected with *C parapsilosis* and *C albicans* had similar birth weights (median 695 (interquartile range (IQR) 622–872) *v* 735 (IQR 650–900) g, respectively), gestational ages at birth (median 25 (IQR 24–26) *v* 25 (IQR 24–26) weeks) and postnatal ages at diagnosis (median 12 (IQR 9–25) *v* 12 (IQR 8–21) days). There was no significant difference between the groups in their prior exposure to a variety of putative risk factors for invasive fungal infection (table 1). However, although overall antibiotic usage was similar, infants with *C parapsilosis* infection were more likely to have received a cephalosporin before diagnosis. There was no significant difference in exposure to antifungal prophylaxis: 7 of 23 infants with *C parapsilosis* infection versus 21 of 50 infants with *C albicans* infection (relative risk (RR) 0.72 (95% CI 0.36 to 1.46)).

Clinical features of infection

C parapsilosis was more likely to be isolated from peripheral blood culture and less likely to be isolated from a urine culture or central vascular line tip culture than *C albicans*. There were no significant differences in the frequency of individual end-organ involvement. However, considerably fewer infants with *C parapsilosis* infection were diagnosed with a deep-seated infection (infection of the kidney, meningitis, peritonitis, osteomyelitis, endocarditis, ophthalmitis, brain abscess, hepatic abscess) than infants with *C albicans* infection (table 2). There were no significant differences in the rates of investigation for the deep-seated infection between the groups.

Treatment and mortality

We found no significant differences in the type or timing of antifungal drug treatment. Empirical antifungal treatment was started before confirmation of the diagnosis in 7 of 23 infants with *C parapsilosis* infection versus 11 of 50 infants with *C albicans* infection: RR 1.38 (95% CI 0.62 to 3.11). Amphotericin B, predominantly in a liposomal formulation, was prescribed for 80% of infants with *C albicans* infection versus 87% of infants with *C parapsilosis* infection. Fluconazole was prescribed for 56% and 43%, and flucytosine for 36% and 30%, respectively (always in combination with amphotericin B). Antifungal resistance testing data were reported for 64% of cases. Only one instance of antifungal resistance (*C parapsilosis* resistant to fluconazole) was reported.

Mortality was not significantly different. Death occurred in 9 of 23 (39%) infants infected with *C parapsilosis* versus 21 of 50 (42%) infected with *C albicans* (RR 0.93 (95% CI 0.51 to 1.71)).

DISCUSSION

Our finding that *C parapsilosis* accounts for about one quarter of all cases of invasive fungal infection in VLBW infants in the UK is consistent with data from North America and elsewhere.[1] As we undertook a surveillance of the whole UK population of VLBW infants over 1 year, this finding is not likely to be due to clustering or temporal variation.

The emergence of *C parapsilosis* as an important pathogen in VLBW infants may be related to changes in neonatal intensive care practices. More extremely preterm infants now survive beyond the first few days after birth and are exposed to invasive procedures that predispose to nosocomial infection. In vitro, *C parapsilosis* proliferates in high concentrations of glucose and

Abbreviations: IQR, interquartile range; VLBW, very low birth weight

Table 1 Prior clinical exposures in very low birthweight infants diagnosed with invasive *Candida* infection

Exposure	No of cases (%)		RR (95% CI)
	C parapsilosis n = 23	*C albicans* n = 50	
Central vascular access	23 (100)	49 (98)	1.02 (0.98 to 1.06)
Parenteral nutrition	23 (100)	49 (98)	1.02 (0.98 to 1.06)
Mechanical ventilation	23 (100)	47 (94)	1.06 (0.99 to 1.14)
Any antibiotics	23 (100)	49 (98)	1.02 (0.98 to 1.06)
Aminoglycosides	18 (78)	45 (90)	0.87 (0.69 to 1.10)
Vancomycin/teicoplanin	20 (87)	38 (76)	1.14 (0.92 to 1.43)
Cephalosporins	20 (87)	31 (62)	1.40 (1.07 to 1.83)
Postnatal steroids	3 (13)	11 (22)	0.59 (0.18 to 1.92)
H_2 receptor antagonists	6 (26)	7 (14)	1.86 (0.70 to 4.93)

can form biofilms on synthetic materials.[2] The use of central venous catheters to deliver parenteral nutrition is a risk factor for invasive fungal infection,[4] but we, and others,[5] did not find a significant difference in the frequency of central venous catheter use between infants infected with *C parapsilosis* and those infected with *C albicans*. We also found that infants with *C parapsilosis* infection were less likely to have evidence of central vascular line colonisation than infants with *C albicans* infection.

We did not find significant differences in exposure to other risk factors for invasive fungal infection between the groups. However, a larger study would be required to detect smaller but potentially important effects of putative risk factors and to allow multivariate analysis to adjust for potential confounding factors. Although our finding of an association between prior exposure to cephalosporins and *C parapsilosis* infection may have been due to chance, a previous study has also suggested that prolonged third-generation cephalosporin use predisposes to *C parapsilosis* infection in VLBW infants.[5] This possible association may be worth investigating further.

We found some evidence to suggest that VLBW infants with *C parapsilosis* had a more benign clinical course with less end-organ involvement than those with *C albicans* infection. Only 9% of infants infected with *C parapsilosis* had evidence of deep-seated infection versus 36% of infants infected with *C albicans*. This difference is unlikely to be due to ascertainment bias, as the reported pattern of investigation for disseminated disease was independent of the *Candida* species identified. Despite the difference in the rate of end-organ involvement, mortality did not differ significantly. We did not attempt to examine whether mortality specifically attributable to invasive fungal infection differed between the groups, because assignment of the cause of death in this population is subjective and subject to bias.

The antifungal susceptibility patterns, antifungal drugs used in treatment and the duration of treatment were similar for both groups of infants. Previous studies have suggested that *C parapsilosis* is more likely than *C albicans* to be tolerant to amphotericin B,[2] but we did not find any instances of amphotericin B resistance in *C parapsilosis* isolates. Amphotericin B remains an appropriate choice of antifungal agent for empirical treatment of invasive fungal infection.

We do not know whether adjunctive aspects of treatment, including the timing of removal of central venous catheters, differed. A study from North America found that VLBW infants with *C parapsilosis* infection were less likely to have early removal of central venous catheters than infants with *C albicans* infection, and speculated that this delay contributed to the high mortality in infants with *C parapsilosis* infection.[5] Further prospective research is needed to explore this possibility.

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Table 2 Organ and system involvement and sites of isolation in very low birthweight infants with invasive *Candida* infection

Site of infection	No of cases (%)		RR (95% CI)
	C parapsilosis n = 23	*C albicans* n = 50	
Peripheral blood	22 (96)	37 (74)	1.29 (1.07 to 1.56)
Urine	2 (9)	18 (36)	0.24 (0.06 to 0.96)
Central vascular line tip	5 (22)	26 (52)	0.42 (0.18 to 0.95)
Skin abscess	1 (4)	13 (26)	0.17 (0.02 to 1.20)
Deep-seated infection	2 (9)	18 (36)	0.24 (0.06 to 0.96)
Renal "fungal balls"	2 (9)	3 (6)	1.45 (0.26 to 8.09)
Meningitis	0	6 (12)	0.16 (0.01 to 2.78)
Peritonitis	1 (4)	5 (10)	0.43 (0.05 to 3.51)
Osteomyelitis	0	1 (2)	0.71 (0.03 to 16.76)
Endocarditis	0	3 (6)	0.30 (0.02 to 5.65)
Ophthalmitis	0	1 (2)	0.71 (0.03 to 16.76)
Brain abscess	0	1 (2)	0.71 (0.03 to 16.76)
Hepatic abscess	0	1 (2)	0.71 (0.03 to 16.76)

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