# Neonatal invasive fungal infection in England 2004–2010

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## Abstract

Rates of invasive fungal infection are highest among neonates, especially those of low birthweight. This study aimed to describe the current epidemiology of invasive neonatal fungal infections in a UK neonatal infection surveillance network. From 2004 to 2010 prospective multicentre surveillance was conducted by 14 neonatal units using a web-based database. Clinicians then completed a standardized pro forma for each positive fungal blood and/or cerebrospinal fluid culture. The overall incidence was 2.4/1000 neonatal unit admissions and was highest among babies <1000 g (extreme low birthweight, 18.8/1000). Only five infants (6%) were >1500 g. The majority of infections were caused by *Candida albicans* (59; 69%) and *Candida parapsilosis* (17; 20%); 33% of infants had received antifungal prophylaxis. Known risk factors (use of central venous catheter, parenteral nutrition, previous antibiotic use) were common among cases. The attributable case fatality rate was 21% (18/84). Extreme low birthweight infants remain at highest risk of invasive fungal infection and prophylaxis should be particularly considered for this group. The number needing to receive prophylaxis to prevent one case varies significantly among units, hence unit-specific decisions are required. Further research is still needed into the optimal empiric and therapeutic strategies.

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## Introduction

Invasive fungal infections (IFIs) are an important cause of morbidity and mortality in preterm or very-low-birthweight infants (VLBW <1500 g). The majority are due to *Candida* species [1]. In the USA an incidence rate of 90/1000 extremely-low-birthweight infants (ELBW <1000 g) was reported between 2004 and 2007 [2], in contrast to a rate of 20/1000 ELBW in the UK in 2004 [3]. Mortality attributable to IFI in neonates ranges from 25 to 55% with neurodevelopmental impairment reported in up to 57% [4,5].

A recent analysis of 137 cases of invasive candidiasis in the USA identified potentially modifiable risk factors including use of central venous catheters, broad-spectrum antibiotics, intravenous lipid emulsion, endotracheal tubes and antenatal antibiotics [2].

There are no recent data on incidence, clinical presentation, risk factors and outcome of IFI in neonates in the UK. The last national surveillance study focused on VLBW infants and was conducted 10 years ago [3]. A recent report from England described the isolates of invasive *Candida* infections in children but had no clinical information [6].

In 2004 a neonatal infection surveillance network (neonIN) was established with the objective of collecting clinical and microbiological data. This study aimed to establish the current epidemiology of neonatal IFIs to enable evidence-based decisions to be made regarding prophylaxis and treatment, and to identify future research directions.

## Material and Methods

An episode of IFI was defined as a positive culture from blood and/or cerebrospinal fluid. Repeatedly positive cultures with the same fungus were considered to represent the same episode if there were <14 days between samples. Anonymized data were prospectively uploaded by each neonatal unit (NNU), and validated with input from laboratory microbiology data. Further clinical data were collected retrospectively using a standardized pro forma for cases recorded between 2004 and 2009, and prospectively for 2010. Local guidelines for prophylaxis including date of implementation were provided by the investigators.

Data were analysed using GRAPHPAD PRISM version 6.00 for Windows (Graphpad Software, La Jolla, CA, USA; www.graphpad.com). Comparison was made with chi-square test for normally distributed categorical data or Mann–Whitney *U*-test when a normal distribution could not be assumed.

NeonIN received research ethics approval in 2005 (05/Q0806/34), each participating centre received separate approval from their local ethics committees.

## Results

Over the 7 years of the study, 14 NNUs reported a total of 98 cases of IFI. The number of participating NNUs increased over the years: seven units between 2004 and 2005, nine between 2006 and 2007, 12 in 2008, 13 in 2009 and 14 in 2010. Twelve of the units were level 3 and two units were level 2 [7]; seven units provided surgery, either general/abdominal and/or cardiac.

### Incidence

Denominator data (live births and neonatal admissions per year, split by gestational age and birthweight) were available for 12 units (reporting 95 cases). The overall incidence was 2.4/1000 NNU admissions. The highest incidence was reported among ELBW infants (18.8/1000 ELBW infants). The incidence in VLBW infants was 10.3/1000 VLBW infants. There was considerable variation between NNUs, ranging from 0.4 to 7.0/1000 NNU admissions. The incidence was highest in 2006 (3.9/1000 NNU admissions) and lowest in 2009 (1.6/1000 NNU admissions) (Fig. 1).

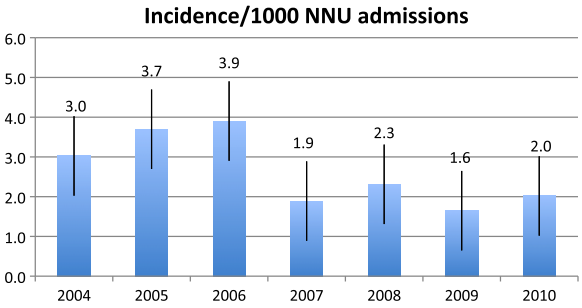


**FIG 1.** Incidence of invasive fungal infections by year (bars indicate 95% confidence intervals).

### Demographics

For 84 infants (86%), demographic and clinical details were available. The median birthweight was 733 g (range 480–2610 g, interquartile range (IQR) 620–860 g), the median gestational age was 25 weeks (range 22–35 weeks). Forty-nine (58%) were male. The birthweight was >1500 g in five infants (6%), four of whom had had abdominal surgery.

### Clinical presentation and laboratory investigations

The median age of IFI was 13 days (range 2–84 days, IQR 8–20 days); early onset infection (within the first 6 days) occurred in 18 cases (21%), only two cases were in the first 3 days of life. The majority of infections (90%) had presented by 30 days of age (94% in ELBW infants) (Fig. 2).

Clinical features and laboratory findings in the week before positive cultures were non-specific. Twenty-seven per cent (23/84) had severe thrombocytopenia ($<50 \times 10^9$/L), 26% (22/84) had neutropenia ($<2.5 \times 10^9$/L) and 62% (51/84) had a rising C-reactive protein. Other common features at presentation are reported in Table 1. During the episode the majority of infants (72/84, 86%) had an elevated C-reactive protein (>10 mg/L, median 57 mg/L; range 20–282 mg/L, IQR 29–113 mg/L) and 87% (73/84) had thrombocytopenia ($<150 \times 10^9$/L; 58% $<50 \times 10^9$/L).

Most infants (76/83, 92%) had received at least one course of antibiotics in the week before the fungal episode was diagnosed, 45% (34/76) had received on or two antibiotics and 55% (42/76) had received two antibiotics. The antibiotics given were narrow spectrum in 47 infants (62%) (benzylpenicillin or flucloxacillin with an aminoglycoside) and broad spectrum in 29 (38%) of 78 infants (cephalosporins, meropenem or tazocin).

The presence of associated risk factors such as invasive ventilation, central vascular catheters and parenteral nutrition was common (Table 2). Twenty (24%) infants were known to be colonized with *Candida* before the invasive episode (although no unit had routine swab-based surveillance in place). The median duration between detection of colonization and invasive disease was 6 days (range 4–26, IQR 5–9 days).