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Candidal versus bacterial late-onset sepsis in very low birthweight infants in Israel: a national survey

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Summary Candidal infections are one of the common causes of late-onset sepsis (LOS) among very low birthweight (VLBW) infants, and are associated with substantial morbidity and mortality. The aim of this study was to evaluate the perinatal and neonatal risk factors for fungal LOS compared with bacterial LOS in VLBW infants. This was a population-based observational study of VLBW infants in 28 neonatal intensive care units across Israel, with information on 11 830 infants born between 1995 and 2002 from the Israeli National VLBW infant database. The study population comprised 3054 infants with one or more episodes of LOS. Univariate analysis and logistic regression models were used to compare perinatal and neonatal risk factors between infants with fungal sepsis only ($N = 179$) and those with bacterial sepsis only ($N = 2630$). The mean birthweight and gestational age of infants with candidal LOS were significantly lower (940 g; 27.1 weeks) than those in the bacterial LOS group (1027 g; 28.3 weeks) ($P < 0.001$). Logistic regression analysis showed that candidal sepsis, in contrast to bacterial sepsis, was independently associated with decreasing gestational age and bronchopulmonary dysplasia (BPD). In addition, BPD only [odds ratio (OR) 1.84; 95% confidence intervals (CI) 1.03–3.23] and BPD with postnatal steroid therapy (OR 2.66; 95%

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CI 1.59—4.46) were independently associated with an increased risk for candidal sepsis.

Introduction

Despite improvement in infection control measures, increased awareness and improved bacteriological identification techniques, infection is still a major cause of morbidity and mortality among very low birthweight (VLBW) infants. Candidal infections have become one of the most common causes of late-onset sepsis (LOS) in VLBW infants.[1,2] The reported incidence of fungal LOS in VLBW infants is 2.6—12.9%[3—5] and is as high as 20% among extremely low birthweight infants.[3,6,7] The crude mortality rate caused by candidal infections is reported to be in the range of 0—50%.[5—11] Among Israeli VLBW infants, 7.2% of infants with candidal sepsis died within 3 days of onset of sepsis, and fungal sepsis was responsible for 15.1% of all early deaths after LOS.[12]

Although blood stream infection is the most common presentation of fungal sepsis, *Candida* spp. can cause meningitis, pneumonia, renal, splenic or liver abscesses, endophthalmitis, osteomyelitis and invasive dermatitis. In addition, there is a trend towards a higher incidence of poor neurological outcome following fungal LOS, particularly in infants with candidal meningitis.[3,4] Numerous perinatal and neonatal factors have been associated with excess risk of sepsis in VLBW infants, and it has been suggested that the risk factors for fungal colonization and infection are similar to those for bacterial colonization and infection.[1,10,13,14]

The aim of this population-based study was to evaluate the effect of perinatal and neonatal risk factors in fungal LOS compared with bacterial LOS in VLBW infants.

Methods

Collection of data

This study is based on an analysis of data collected by the Israel Neonatal Network on VLBW infants born in Israel between January 1995 and December 2002. All 28 neonatal units in Israel participate in data collection for the National VLBW Infant Database (Appendix 1). All live-born infants receive a unique identification number at birth. Patient information received by the database coordinator is cross-checked against the national birth registry and data from any missing infant are requested from the birth hospital. A structured form was completed for each infant. The data collected included parental demographic details, maternal pregnancy history and antenatal care, details of the delivery, the infant's status at delivery, diagnoses, procedures and complications during hospitalization, and outcome at discharge. An operating manual and standard definitions are used by all the neonatal units.[2]

Definitions

Definitions used conform to those of the Vermont Oxford Neonatal Database.[2,15] LOS was defined as positive microbial growth on one or more bloodstream cultures obtained after 72 h of life with accompanying clinical signs of sepsis. All microbial growths in bloodstream cultures were reported. The number of events of LOS, the age at infection and the organisms cultured were recorded. The diagnosis of sepsis due to coagulase-negative staphylococci (CNS) required: (a) clinical signs of sepsis, (b) positive bloodstream culture for CNS, and (c) intravenous antibacterial therapy for at least five days after obtaining blood culture, or until death occurring within five days after obtaining blood culture.[2,15] Whenever CNS and another pathogen were identified in the same blood culture, only the other pathogen was recorded in the database. The age of onset of sepsis was considered to be the day on which the first blood culture for the event was obtained. Information on antimicrobial susceptibility and antibiotic therapy are not recorded in the database.

Gestational age (GA) was determined according to date of last menstrual period and early fetal ultrasonographic findings when available. Small for gestational age (SGA) was defined as birthweight >2 SD below the mean weight for GA according to intrauterine growth charts of Usher and McLean.[16] Respiratory distress syndrome (RDS) was diagnosed according to clinical and radiological criteria and pulmonary air leak included pneumothorax and/or pulmonary interstitial emphysema. Necrotizing enterocolitis (NEC) was diagnosed by the presence of clinical and radiological characteristics according to the criteria of Bell *et al.*[17] Only definite NEC