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Using a Count of Neonatal Morbidities to Predict Poor Outcome in Extremely Low Birth Weight Infants: Added Role of Neonatal Infection

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Abstract

OBJECTIVE—A count of 3 neonatal morbidities (bronchopulmonary dysplasia, brain injury, and severe retinopathy of prematurity) strongly predict the risk of death or neurosensory impairment in extremely low birth weight infants who survive to 36 weeks' postmenstrual age. Neonatal infection has also been linked with later impairment. We examined whether the addition of infection to the count of 3 neonatal morbidities further improves the prediction of poor outcome.

METHODS—We studied 944 infants who participated in the Trial of Indomethacin Prophylaxis in Preterms and survived to 36 weeks' postmenstrual age. Culture-proven sepsis, meningitis, and stage II or III necrotizing enterocolitis were recorded prospectively. We investigated the incremental prognostic importance of neonatal infection by adding terms for the different types of infection to a logistic model that already contained terms for the count of bronchopulmonary dysplasia, brain injury, and severe retinopathy. Poor outcome at 18 months of age was death or survival with 1 or more of the following: cerebral palsy, cognitive delay, severe hearing loss, and bilateral blindness.

RESULTS—There were 414 (44%) infants with at least 1 episode of infection or necrotizing enterocolitis. Meningitis and the presence of any type of infection added independent prognostic information to the morbidity-count model. The odds ratio associated with infection or necrotizing enterocolitis in this model was 50% smaller than the odds ratio associated with each count of the other 3 neonatal morbidities. Meningitis was rare and occurred in 22 (2.3%) of 944 infants.

CONCLUSIONS—In this cohort of extremely low birth weight infants who survived to 36 weeks' postmenstrual age, neonatal infection increased the risk of a late death or survival with neurosensory impairment. However, infection was a weaker predictor of poor outcome than bronchopulmonary dysplasia, brain injury, and severe retinopathy.

Keywords

extremely low birth weight infant; infection; bronchopulmonary dysplasia; brain injury; retinopathy; neurosensory impairment

Advances in perinatal and neonatal intensive care have reduced the mortality rate of extremely low birth weight (ELBW) infants, but ELBW survivors remain at high risk of neurodevelopmental impairments, such as cerebral palsy, cognitive delay, deafness, and blindness.[1–3] Parents want to know whether these adverse outcomes are likely to affect their children and prefer clinicians to provide them with reliable medical information on their infants' prognosis.[4] To be able to respond to parental questions and to anticipate special health care needs, clinicians need valid evidence that allows them to estimate the risk of future impairment with reasonable accuracy.

Our ability to predict long-term outcome is limited during the first few days and weeks after birth.[5] Because of prolonged hospitalizations, ELBW infants are at ongoing risk for medical morbidities and other adverse events that may greatly influence their prognosis.[5–7] A count of 3 common neonatal morbidities (bronchopulmonary dysplasia [BPD], brain injury, and severe retinopathy of prematurity [ROP]) strongly predicts the risk of a late death or neurosensory impairment in ELBW infants who survive to 36 weeks' postmenstrual age. Compared with children who remain free of these adverse events, having 1 of the 3 morbidities approximately doubles the risk of poor outcome at 18 months of age, while having 2 morbidities approximately triples it.[7]

Many ELBW infants have at least 1 episode of early or late-onset infection during their initial hospital stay.[8,9] Neonatal infections and necrotizing enterocolitis (NEC) have been linked with an increased risk of neurodevelopmental impairment in ELBW survivors.[10–15] However, the prognostic importance of infection relative to the other 3 neonatal morbidities remains

uncertain. We undertook this study to examine whether adding infection and NEC to the prognostic count of BPD, brain injury, and severe ROP further improves the prediction of poor outcomes in ELBW infants at 18 months' corrected age.

METHODS

Study Population

Infants with birth weights of 500 to 999 g who were born between January 1996 and March 1998 and participated in the Trial of Indomethacin Prophylaxis in Preterms (TIPP) were included in this analysis.[16] The research ethics boards of all 32 clinical centers (located in Canada, the United States, Australia, New Zealand, and Hong Kong) approved the trial protocol. Written informed consent was obtained from a parent or guardian of each infant. Because infants who die early cannot develop BPD or severe ROP, only infants who survived to 36 weeks' postmenstrual age were eligible for the present study.

BPD, Brain Injury, and Severe ROP

BPD, brain injury, and severe ROP were prespecified secondary outcomes in the TIPP study. BPD was defined as the need for supplemental oxygen at 36 weeks' postmenstrual age. Brain injury was defined by the presence of at least 1 of the following findings on cranial ultrasound scans: echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage.[7,16] ROP was diagnosed according to the international classification at the time of TIPP enrollment.[17,18] Unilateral or bilateral ROP of stages 4 and 5 was considered severe, as was ROP in infants who received cryotherapy or laser therapy in at least 1 eye.

Sepsis, Meningitis, and NEC

In the TIPP study, we recorded prospectively all episodes of neonatal sepsis and meningitis that were confirmed by the finding of a blood and/or cerebrospinal fluid culture growing bacteria, fungi, or viruses. The decision to obtain blood or cerebrospinal fluid for culture was at the discretion of the local clinicians. NEC was a prespecified secondary outcome and diagnosed during surgery, at autopsy, or by a finding of pneumatosis intestinalis, hepatobiliary gas, or free intraperitoneal air on radiography.

Outcomes at 18 Months' Corrected Age

The primary outcome in the TIPP study was death before 18 months' corrected age or the presence in survivors of 1 or more of the following: cerebral palsy, cognitive delay, hearing loss requiring amplification and bilateral blindness.16 The same long-term composite outcome and its components were used in this study. All 18-month assessments were performed prospectively according to a standardized protocol. Cerebral palsy was diagnosed if the child had nonprogressive motor impairment characterized by abnormal muscle tone and decreased range or control of movements. Cognitive delay was defined as a Mental Development Index score below 70 on the Bayley Scales of Infant Development II.[19] The score was assumed to be <70 if the child could not be tested because of severe developmental delay. Audiometry was performed to determine the presence or absence of hearing loss. A central adjudication committee that was unaware of the group assignments reviewed the results of audiologic tests for all infants with potential deafness whose hearing had not been amplified. Blindness was defined as a corrected visual acuity of <20/200. Follow-up was targeted for 18 months' corrected age, but the protocol allowed a window of 18 to 21 months (12–21 months for audiometry). Efforts to conduct assessments continued beyond a corrected age of 21 months to maximize ascertainment of the long-term outcome.

Statistical Analysis

The univariate relationships between the various types of infections and poor 18-month outcome were expressed as odds ratios (ORs), with *P* values derived from the Fisher's exact test. We used a previously constructed logistic model that was developed to improve the prediction of poor outcome at 18 months in ELBW infants.7 This model contains terms for the count of 3 neonatal morbidities (BPD, brain injury, and severe ROP).[7] In addition, we investigated the incremental prognostic importance of neonatal infection by adding terms for sepsis, meningitis with or without sepsis, NEC, and neonatal infection (sepsis and/or meningitis) or NEC to this logistic model. The *P* value associated with the additional prognostic factor was based on the Wald χ^2.

RESULTS

Study Population

Of the 1202 infants who were enrolled in the TIPP study, 199 died before 36 weeks' postmenstrual age. Adequate data for analysis of the 18-month composite outcome were available for 944 (96.4%) of the 1003 eligible infants. A total of 910 infants had complete data for the prognostic count of BPD, brain injury, and severe ROP.[7] Their mean gestational age (SD) was 26.2 weeks (1.8) and mean (SD) birth weight was 793 g. (127) 7 Fifty percent of the infants were girls (n = 456), and 82% (n = 745) were exposed to antenatal corticosteroids.[7] Additional maternal and infant baseline characteristics of this analysis cohort were reported previously.[7]

Univariate Relationships Between Neonatal Infections and Outcome at 18 Months

During their stay in the NICU, 414 (44%) of 944 infants who survived to 36 weeks' postmenstrual age had at least 1 episode of sepsis, meningitis, and/or NEC: 378 (40%) had culture proven sepsis, 22 (2.3%) had culture proven meningitis, and 83 (8.8%) developed NEC of Bell stages II or III. Neonatal sepsis, meningitis, and NEC were all associated with a poor 18-month outcome (Table 1). Meningitis with or without sepsis showed the strongest association with the 18-month outcome but was a relatively rare finding. Sepsis was the most prevalent type of infection but less predictive of poor long-term outcome than meningitis or NEC.

Table 1 shows the associations between different types of infection, the composite outcome of death after 36 weeks or impairment at 18 months, and the individual components that make up this composite outcome.

Prediction of Poor 18-Month Outcome According to Morbidity Count: The Added Role of Neonatal Infection

Figure 1 shows the observed probabilities of a late death or impairment at 18 months by morbidity count, for infants with and without different types of infection. The overall probability of a poor 18-month outcome in the study cohort before the application of the morbidity-count model was 35%. The risk of a poor 18-month outcome increased steadily with the number of neonatal morbidities, both in the absence and presence of infection. Infants with infection had slightly higher rates of poor outcome than infants who did not acquire infections during their stay in the NICU.

Table 2 summarizes the incremental contribution of different types of infection to the prognostic count of BPD, brain injury, and severe ROP. A history of culture-proven sepsis, meningitis, or NEC provided independent and significant prognostic information when added to the morbidity-count model. However, the OR associated with infection or NEC was only

1.4 (95% confidence interval [CI]: 1.0 –1.8; $P = .04$). In contrast, the OR associated with each count of the 3 morbidities in this model was 2.8 (95% CI: 2.3–3.4).

DISCUSSION

This study confirms previous reports that neonatal sepsis, meningitis, and NEC increase the risk of a poor neurodevelopmental outcome in ELBW infants.[10–15] However, with the exception of meningitis, neonatal infections were weaker predictors of a late death or of survival with impairment than 3 other common neonatal morbidities (BPD, brain injury, and severe ROP).

It was suggested that neonatal infections may predispose very preterm infants to the development of BPD, brain injury, and ROP and hence may determine long-term outcome via these intermediate morbidities.[20–22] This hypothesis was partially supported by our data because the univariate associations of infection with long-term outcome were slightly stronger than their corresponding associations in the model that also contained the morbidity count. However, most of the prognostic value of infection could not be explained by a greater risk of BPD, brain injury, and severe ROP in infants with infection compared with infants who remained free of infection. Furthermore, the addition of infection to the model containing the morbidity count did not affect the strength of the relationship between the morbidity count and neurodevelopmental outcome. This implies that the modest incremental prognostic information derived from the presence or absence of infection was independent from the prognostic contribution of the morbidity count.

The long-term prognosis of extremely preterm infants changes with postnatal age and the development of morbidities during the primary hospitalization.[6]

Even the smallest and most immature infants have a favorable long-term prognosis if they survive the NICU stay without serious adverse events and morbidities, such as BPD or severe ROP.[6,7] Unfortunately, many ELBW infants develop multiple morbidities if they survive long enough to reach 36 weeks' postmenstrual age. A simple count of BPD, brain injury, and severe ROP is a powerful predictor in such infants of a late death or survival with neurodevelopmental impairment.[7] Although neonatal infection or NEC was a weaker predictor of long-term outcome than the 3 other neonatal morbidities in the present study, rates of poor outcome were higher among infants with infection than without infection. Therefore, a strong incentive remains to prevent as many nosocomial infections as possible during the primary hospitalization of ELBW infants.

The strengths of our study include the size and international scope of our cohort. In addition, all data were collected prospectively according to a standardized protocol, and the follow-up rate at 18 months was very high. An obvious limitation is the fact that the study participants were enrolled in a randomized clinical trial.[16] Consequently, the study population may not be representative of all ELBW infants who are admitted to a NICU. However, the baseline characteristics, the rates of BPD, brain injury, severe ROP, and the rates of impairments at 18 months were comparable to regional cohorts that were not derived from a clinical trial population.[2,23,24] In addition, the rates of sepsis, meningitis, and NEC in this study were also comparable with other recent studies that examined the role of neonatal infection in survivors to 18 months' corrected age.[11,13] We recognize that the prevalence of meningitis may have been underestimated in those recent studies and in ours.[25]

Like every posthoc analysis, our study generates hypotheses that should be confirmed by other investigators. The morbidity-count model has already been validated in 2 separate regional cohorts of ELBW infants.[23,24] In the current study, we planned a priori to examine only the additional prognostic effects of neonatal sepsis, meningitis, and NEC. No other variables were

added to the morbidity-count model. Therefore, the risk of a type I error arising from multiple hypothesis tests was fairly low.

CONCLUSIONS

Neonatal infection or NEC adds to the prediction of a late death or survival with neurosensory impairment in ELBW survivors. However, with the exception of meningitis, infections are weaker predictors of poor long-term outcome than BPD, brain injury, and severe ROP.

What's Known on This Subject

A count of BPD, brain injury, and severe ROP improves the prediction of long-term outcome in ELBW infants. Infection during the initial hospitalization has also been linked with adverse neurodevelopmental outcome.

What This Study Adds

Infection increases the risk of poor outcome. However, infection is a weaker predictor of outcome than BPD, brain injury, and ROP.

Abbreviations

ELBW	extremely low birth weight
BPD	bronchopulmonary dysplasia
ROP	retinopathy of prematurity
NEC	necrotizing enterocolitis
TIPP	Trial of Indomethacin Prophylaxis in Preterms
OR	odds ratio
CI	confidence interval

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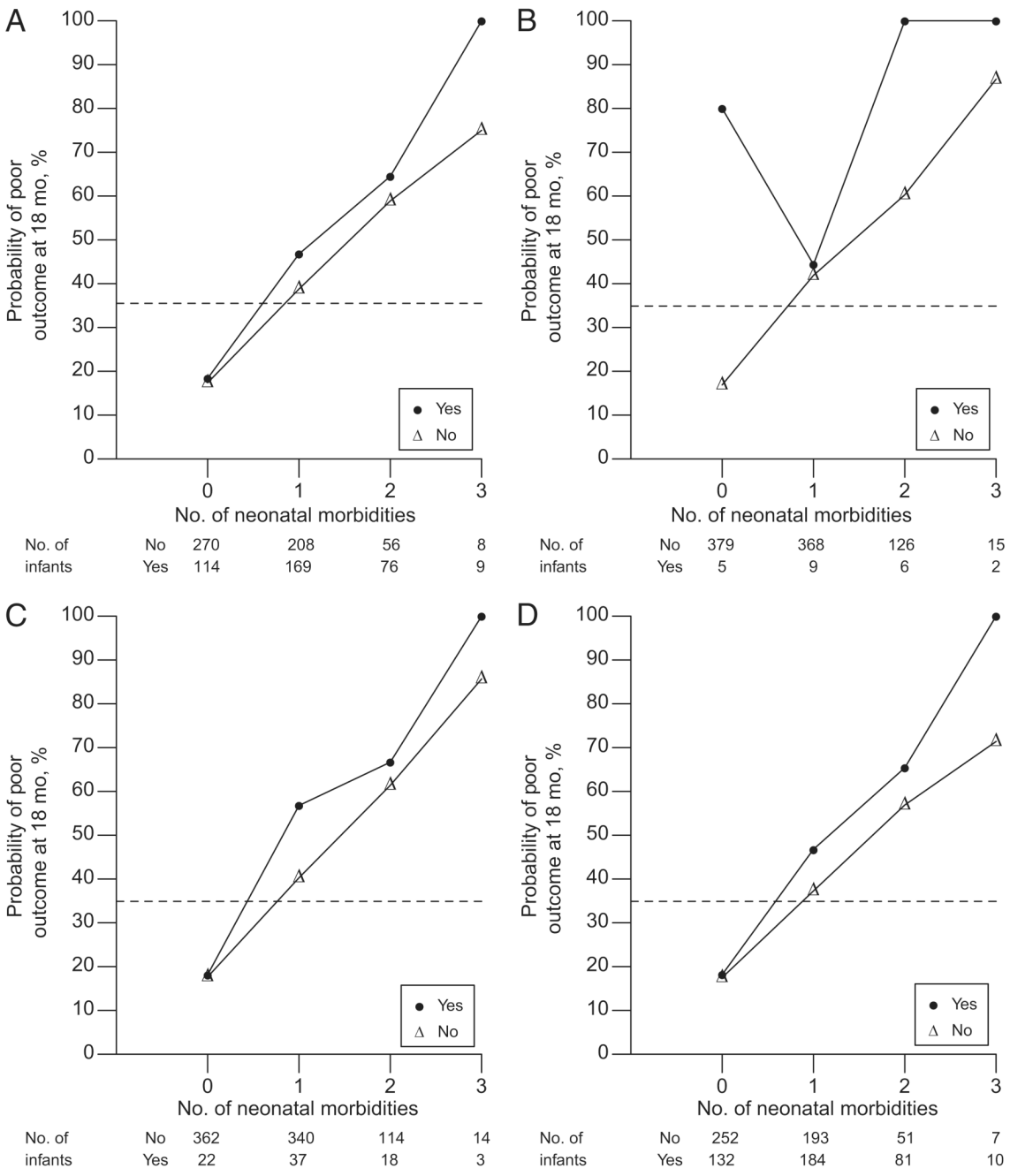

FIGURE 1.

Probability of death after 36 weeks' postmenstrual age or survival with neurodevelopmental impairment at 18 months by morbidity count, stratified according to the presence or absence of sepsis (A), meningitis (B), NEC (C), and infection or NEC (D). The dotted lines indicate the overall probability of a poor 18-month outcome (35%).

TABLE 1

Univariate Relationships Between Types of Neonatal Infections and Outcomes at 18 Months

Type of Infection	Poor 18-mo Outcome: Death or Neurosensory Impairment			Components of Poor 18-mo Outcome: Death and Individual Impairments, *n*/*N* (%)				
	n/*N* (%)	OR (95% CI)	*P*	Death	CP	MDI<70	Deaf	Blind
Sepsis								
Present	161/378 (43)	1.7 (1.3–2.2)	<.0001	23/394 (5.8)	56/369 (15)	106/351 (30)	12/359 (3.3)	10/368 (2.7)
Absent	172/566 (30)			14/596 (2.3)	57/575 (10)	129/550 (23)	8/563 (1.4)	6/569 (1.1)
Meningitis								
Present	16/22 (73)	5.1 (2.0–13.1)	.0008	2/24 (8.3)	4/21 (19)	12/19 (63)	1/21 (4.8)	1/21 (4.8)
Absent	317/922 (34)			35/966 (3.6)	109/923 (12)	223/882 (25)	19/901 (2.1)	15/916 (1.6)
NEC								
Present	43/83 (52)	2.1 (1.4–3.3)	.0012	9/86 (10)	11/77 (13)	30/74 (41)	2/73 (2.7)	0/77 (0.0)
Absent	290/861 (34)			28/904 (3.1)	102/867 (12)	205/827 (25)	18/849 (2.1)	16/860 (1.9)
Any infection								
Present	177/414 (43)	1.8 (1.4–2.4)	<.0001	24/432 (5.6)	59/405 (15)	121/386 (31)	12/393 (3.1)	10/404 (2.5)
Absent	156/530 (29)			13/558 (2.3)	54/539 (10)	114/515 (22)	8/529 (1.5)	6/533 (1.1)

CP indicates cerebral palsy; MDI, Mental Development Index.

TABLE 2

Prediction of Poor Outcome at 18 Months: Additional Contribution of Neonatal Infections to the Prognostic Count of BPD, Brain Injury, and Severe ROP

Type of Infection	*n*/*N* (%)	OR (95%CI)	*P*
Sepsis	368/910 (40)	1.3 (1.0–1.8)[a]	.07
Meningitis	22/910 (2.4)	4.0 (1.4–11.0)[b]	.008
NEC	80/910 (8.8)	1.6 (1.0–2.6)[c]	.08
Any infection	407/910 (45)	1.4 (1.0–1.8)[d]	.04

[a] In this model, the OR (95% CI) associated with each count of the 3 neonatal morbidities was 2.8 (2.3–3.4).

[b] In this model, the OR (95% CI) associated with each count of the 3 neonatal morbidities was 2.9 (2.3–3.5).

[c] In this model, the OR (95% CI) associated with each count of the 3 neonatal morbidities was 2.9 (2.3–3.5).

[d] In this model, the OR (95% CI) associated with each count of the 3 neonatal morbidities was 2.8 (2.3–3.4).