Impact of Bronchopulmonary Dysplasia, Brain Injury, and Severe Retinopathy on the Outcome of Extremely Low-Birth-Weight Infants at 18 Months

Results From the Trial of Indomethacin Prophylaxis in Preterms

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Context Despite more than 2 decades of outcomes research after very preterm birth, clinicians remain uncertain about the extent to which neonatal morbidities predict poor long-term outcomes of extremely low-birth-weight (ELBW) infants.

Objective To determine the individual and combined prognostic effects of bronchopulmonary dysplasia (BPD), ultrasonographic signs of brain injury, and severe retinopathy of prematurity (ROP) on 18-month outcomes of ELBW infants.

Design Inception cohort assembled for the Trial of Indomethacin Prophylaxis in Preterms (TIPP).

Setting and Participants A total of 910 infants with birth weights of 500 to 999 g who were admitted to 1 of 32 neonatal intensive care units in Canada, the United States, Australia, New Zealand, and Hong Kong between 1996 and 1998 and who survived to a postmenstrual age of 36 weeks.

Main Outcome Measures Combined end point of death or survival to 18 months with 1 or more of cerebral palsy, cognitive delay, severe hearing loss, and bilateral blindness.

Results Each of the neonatal morbidities was similarly and independently correlated with a poor 18-month outcome. Odds ratios were 2.4 (95% confidence interval [CI], 1.8-3.2) for BPD, 3.7 (95% CI, 2.6-5.3) for brain injury, and 3.1 (95% CI, 1.9-5.0) for severe ROP. In children who were free of BPD, brain injury, and severe ROP the rate of poor long-term outcomes was 18% (95% CI, 14%-22%). Corresponding rates with any 1, any 2, and all 3 neonatal morbidities were 42% (95% CI, 37%-47%), 62% (95% CI, 53%-70%), and 88% (64%-99%), respectively.

Conclusion In ELBW infants who survive to a postmenstrual age of 36 weeks, a simple count of 3 common neonatal morbidities strongly predicts the risk of later death or neurosensory impairment.

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HEALTH PROFESSIONALS AND parents of very preterm infants fear the development of bronchopulmonary dysplasia (BPD), brain injury, and severe retinopathy of prematurity (ROP) because these neonatal morbidities are risk factors for neurosensory impairment in childhood. Bronchopulmonary dysplasia has been associated with low psychomotor development index scores on the Bayley Scales of Infant Development II,[1,2] neurologic abnormalities[3] including cerebral palsy,[4] and poor mental development.[2,3] Ultrasonographic signs of brain injury such as severe periventricular and intraventricular hemorrhage, periventricular leukomalacia, and ventriculomegaly also increase the risks of mental[2,5] and motor[2-7] impairments. Severe ROP is associated with later visual impairment[7,8] and functional disability.[9] However, it has remained uncertain to what degree the presence or absence of 1 or more of these neonatal complications affects the overall prognosis of very preterm infants who survive to near term. A better understanding of the predictive value of these neonatal morbidities would improve the ability to counsel parents and to anticipate special needs.

We undertook this study to examine the individual and combined prognostic impact of BPD, brain injury, and severe ROP on the 18-month outcome

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of extremely low-birth-weight (ELBW) infants who survive to a postmenstrual age of 36 weeks.

METHODS

Study Population

Infants with birth weights of 500 to 999 g were enrolled in the international Trial of Indomethacin Prophylaxis in Preterms (TIPP) between 1996 and 1998.[10] The research ethics boards of all 32 participating clinical centers (located in Canada, the United States, Australia, New Zealand, and Hong Kong) approved the trial protocol, and written informed consent was obtained from a parent or guardian of each infant. Since infants who die early in their course in the neonatal intensive care unit cannot develop the morbidities of interest, only infants who survived to a postmenstrual age of 36 weeks were eligible for the current study.

Neonatal Morbidities

Bronchopulmonary dysplasia, brain injury, and severe ROP were prespecified secondary outcomes in the TIPP study. All data were collected prospectively in a standardized fashion. Bronchopulmonary dysplasia was defined as the need for supplemental oxygen at a postmenstrual age of 36 weeks.[11] Cranial ultrasonography was recommended between days 5 and 8, between days 21 and 28, and between 34 and 36 weeks postmenstrual age if the infant was still in the study center. The scans were read locally. Copies of the written reports were sent to the coordinating center. Several types of lesions were considered as a group because they all indicate probable brain injury[6]; these included echodense intraparenchymal lesions, periventricular leukomalacia, porencephalic cysts, and ventriculomegaly with or without intraventricular hemorrhage. This cluster of lesions includes periventricular and intraventricular hemorrhages of grades 3 and 4.[12] Retinopathy was diagnosed according to the international classification.[13,14] Unilateral or bilateral ROP of stages 4 and 5 were considered severe. Infants were also classified as having severe ROP if they received cryotherapy or laser therapy in at least 1 eye. Infants were screened for ROP according to local nursery protocols.

Outcomes at a Corrected Age of 18 Months

In the TIPP study, the primary composite outcome was death before a corrected age of 18 months or the presence in survivors of 1 or more of the following: cerebral palsy, cognitive delay, hearing loss requiring amplification, and bilateral blindness.[10] The same long-term composite outcome was used in the current analysis. 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 (2 SDs below the mean of 100) on the Bayley Scales of Infant Development II.[15] The score was assumed to be less than 70 if the child could not be tested due to severe developmental delay. Sound field audiometry was performed to determine the presence or absence of hearing loss. A central adjudication committee blinded to any clinical data reviewed the audiological test results from all infants with potential deafness whose hearing had not been amplified. Infant blindness was defined as a corrected visual acuity less than 20/200. Follow-up was targeted for a corrected age of 18 months, but the protocol allowed a window of 18 to 21 months (12 to 21 months for audiometry). Efforts to conduct assessments continued beyond a corrected age of 21 months to maximize completeness. Home visits or assessments in nonstudy facilities were permitted when necessary.

The confirmation of either death or any 1 of the 4 types of impairment determined the presence of the composite primary outcome, but its absence required confirmation that the infant had survived without any impairment. Since a single missing component of the follow-up assessment would result in a designation of "missing" for the composite outcome, detailed a priori criteria were used to define what constituted "adequate evidence" for the presence or absence of each component of the primary outcome.[10]

Statistical Analysis

Logistic function regression was used to investigate the relationship between the 3 neonatal morbidities and the outcome at 18 months.[16] Initially, a stepwise model was constructed including 3 indicator variables for the presence or absence of BPD, brain injury, and severe ROP. This model assumes that the neonatal morbidities provide independent, additive prognostic information on the log odds scale. The regression coefficient associated with each term in the model is a log odds ratio. The potential for a lack of prognostic independence among the neonatal morbidities was investigated by adding second-order interactions (as product variables between pairs of neonatal morbidities) to the model. The significance of the prognostic information of any term, or group of terms, was tested using a χ^2 test. A logistic model was also constructed using the number of neonatal morbidities present. Exact 95% confidence intervals were computed around the observed proportions of poor outcome at 18 months. All analyses were carried out with SAS v6.12 (SAS Institute Inc, Cary, NC); *P* values were 2-sided and considered significant if $<.05$.

RESULTS

Study Population and Outcomes at a Corrected Age of 18 Months

In the TIPP study, 1202 infants with a birth weight of 500 through 999 g were enrolled; 1003 survived to 36 weeks postmenstrual age. All neonatal outcomes were known for 967 infants and adequate data for analysis of the composite 18-month outcomes were available for 910. The baseline characteristics of the 910 study infants and their mothers are summarized in TABLE 1. Overall, 323 infants (35%) had a poor outcome at 18 months. Thirty-four infants (4%) died after a postmenstrual

age of 36 weeks. Of the 876 survivors, 110 (13%) developed cerebral palsy, 229 (26%) had cognitive delay, 20 (2%) had hearing loss requiring amplification, and 16 infants (2%) had bilateral blindness.

Univariate Relationships Between Neonatal Morbidities and Outcome at 18 Months

During the neonatal period, 409 (45%) of the 910 infants in the analysis cohort developed BPD, 194 (21%) had ultrasonographic evidence of brain injury, and 89 (10%) had severe ROP. Each of these 3 neonatal morbidities was strongly associated with a poor 18-month outcome (TABLE 2). Severe ROP showed the strongest association with 18-month outcome but was a relatively uncommon neonatal finding. Bronchopulmonary dysplasia was the most prevalent neonatal morbidity but somewhat less predictive of long-term outcome than severe ROP or brain injury. Table 2 shows the association between each of the 3 morbidities and the individual components of the composite 18-month outcome.

Table 1. Baseline Characteristics of Study Infants and Mothers

Characteristic	No. (%)
Mothers	
No.	910
Age, mean (SD), y	28.9 (6.9)
Race	
White	631 (70)
Black	129 (14)
Asian	56 (6)
Other/unknown	94 (10)
Education	
Less than high school	277 (31)
Completed high school	271 (30)
Some college or university	349 (39)
Single parent	246 (27)
Received antenatal steroids	745 (82)
Infants	
No.	910
Birth weight, mean (SD), g	793 (127)
Gestational age, mean (SD), wk	26.2 (1.8)
Female sex	456 (50)
Singleton birth	679 (75)

Prediction Models

TABLE 3 summarizes the results of fitting a logistic model to the 18-month outcome. This model contained indicator variables for the 3 separate neonatal morbidities and estimated the independent prognostic information that was provided by each of the neonatal morbidities after adjustment for any intercorrelation. Each of the morbidities had a significant effect on the risk of poor outcome at 18 months. In addition, none of the second-order interactions between pairs of neonatal morbidities was significant. The *P* value for interactions as a whole was .36. This suggests that the 3 neonatal morbidities provided independent prognostic information. This prognostic independence, together with the observation that the odds ratios associated with each of the neonatal morbidities were similar in size, implies that a very simple predictive model based solely on the number of morbidities that are present would fit the observed data well. The estimated coefficients for this model are shown in Table 3. The model suggests an odds ratio of 2.9 (95% confidence interval, 2.4-3.5) for each additional neonatal morbidity.

Prediction of Poor Outcome at 18 Months

TABLE 4 shows the observed rates of poor 18-month outcome in subgroups of infants with different combinations of neonatal morbidities, beginning with those infants who remained free of all morbidities, and ending with the small group of infants who developed all 3 morbidities. All possible combinations were considered, including single morbidities and all possible pairs of morbidities. In the same table we also show the corresponding rates of poor 18-month outcome that were predicted by 2 logistic models, one including terms for the presence of the individual morbidities and the other based solely on a count of the 3 morbidities. The observed risk of poor long-term outcome was 18% (95% confidence interval, 14%-22%) in infants without any of the 3 neonatal morbidities. This increased to an average risk of 42% (37%-47%) with any 1 of the morbidities, 62% (53%-70%) with any 2, and 88% (64%-99%) with all 3. Each of the 3 morbidities, and each pair of morbidities, contributed a comparable amount of prognostic information. The logistic model with terms for the presence of the individual morbidities generated probabilities of a poor 18-month outcome that fit the observed data very closely (Table 4). Importantly, almost the same predictive accuracy could be achieved with a model that is based on a simple morbidity count (Table 4). The fit of this latter model is shown in FIGURE 1.

Table 2. Univariate Relationships Between Individual Neonatal Morbidities and Outcomes at 18 Months

Neonatal Morbidity		Poor 18-Month Outcome: Death or Neurosensory Impairment*			Components of Poor 18-Month Outcome: Death and Individual Impairments, No./Total (%)				
		No./Total (%)	OR (95% CI)	*P* Value	Death	CP	MDI <70	Deaf	Blind
BPD	Present	193/409 (47)	2.5 (1.9-3.4)	<.001	28/409 (6.8)	64/381 (17.0)	135/374 (36.0)	13/370 (3.5)	7/377 (1.9)
	Absent	130/501 (26)			6/501 (1.2)	46/494 (9.3)	94/487 (19.0)	7/489 (1.4)	9/491 (1.8)
Brain injury	Present	116/194 (60)	3.7 (2.6-5.2)	<.001	17/194 (8.8)	63/177 (36.0)	73/172 (42.0)	5/172 (2.9)	5/175 (2.9)
	Absent	207/716 (29)			17/716 (2.4)	47/698 (6.7)	156/689 (23.0)	15/687 (2.2)	11/693 (1.6)
Severe ROP	Present	58/89 (65)	3.9 (2.4-6.4)	<.001	9/89 (10.0)	19/80 (24.0)	34/69 (49.0)	3/78 (3.8)	12/80 (15.0)
	Absent	265/821 (32)			25/821 (3.0)	91/795 (12.0)	195/792 (25.0)	17/781 (2.2)	4/788 (0.5)

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; CP, cerebral palsy; MDI, Mental Development Index; OR, odds ratio; ROP, retinopathy of prematurity.
*The rate of poor outcome in the entire cohort was 323/910 (35%).

Effect of Birth Weight, Gestational Age, Maternal Race, and Maternal Education

We also investigated whether the prognostic value of the morbidity count was influenced by birth weight (500-749 vs 750-999 g), gestational age (≤26 vs ≥27 weeks), maternal race (white vs nonwhite), and maternal education (completed high school vs less than high school). For each of these risk factors we fitted a logistic model that contained terms for the direct effects of the morbidity count, the respective risk factor, and an interaction. The prognostic effect of the morbidity count remained strong ($P<.001$) in all 4 models. None of the interactions was significant: the smallest P value for an interaction in these 4 analyses was .61. This indicates that the morbidity count predicted the 18-month outcome equally well in each of the 2 strata for birth weight, gestational age, maternal race, and maternal education (FIGURE 2). Birth weight ($P=.002$) and maternal race ($P<.001$) added prognostic information to the morbidity count, but gestational age ($P=.74$) and maternal education ($P=.93$) did not (Figure 2).

Table 3. Logistic Models

Model Type, Terms	Regression Coefficient (SE)	OR (95% CI)	*P* Value
Individual morbidities			
Intercept	−1.44 (0.12)		
BPD	0.87 (0.15)	2.4 (1.8-3.2)	<.001
Brain injury	1.32 (0.18)	3.7 (2.6-5.3)	<.001
Severe ROP	1.13 (0.25)	3.1 (1.9-5.0)	<.001
Morbidity count*			
Intercept	−1.47 (0.12)		
Morbidity count	1.05 (0.10)	2.9 (2.4-3.5)	<.001

Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; OR, odds ratio; ROP, retinopathy of prematurity.
*Comprises the number present of BPD, brain injury, and severe ROP.

Table 4. Observed and Predicted Poor Outcome at 18 Months, by Combination of Neonatal Morbidity

	Probability of Poor Outcome at 18 Months		
		Logistic Model Prediction	
Neonatal Morbidities	Observed Data, No./Total (%) [95% CI]	Individual Morbidities, %	Morbidity Count, %
None	68/384 (18) [14-22]	19	19
Single morbidity			
BPD	103/269 (38)	36	
Brain injury	47/92 (51)	47	
Severe ROP	8/16 (50)	42	
Overall	158/377 (42) [37-47]	39	40
2 Morbidities			
BPD + brain injury	47/76 (62)	68	
BPD + severe ROP	28/47 (60)	64	
Brain injury + severe ROP	7/9 (78)	73	
Overall	82/132 (62) [53-70]	67	65
BPD + brain injury + severe ROP	15/17 (88) [64-99]	87	85
All patients	323/910 (35)		

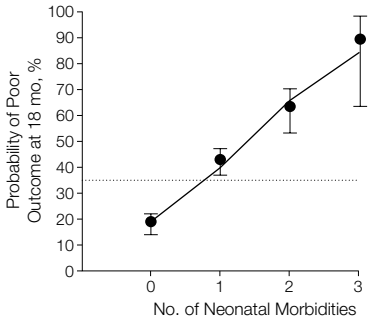
Abbreviations: BPD, bronchopulmonary dysplasia; CI, confidence interval; ROP, retinopathy of prematurity.

COMMENT

Bronchopulmonary dysplasia, ultrasonographic signs of brain injury, and severe ROP were each only modest predictors of a poor long-term outcome in this international cohort of ELBW infants who survived to a postmenstrual age of 36 weeks. However, we found that these 3 neonatal morbidities contributed similarly and independently from each other to the prediction of the infants' status at a corrected age of 18 months. Therefore, it was possible to develop a very simple predictive model based solely on the number of neonatal morbidities. Counting whether an infant had none, any 1, any 2, or all 3 of these neonatal morbidities greatly improved the prediction of a late death or of survival with neurosensory impairment.

Bronchopulmonary dysplasia, brain injury, and severe ROP are known risk factors for poor long-term outcome in very preterm infants,[1-9] which is why we chose those 3 morbidities as predictor variables in the present study. Indeed, our individual estimates of risks associated with either BPD, ultrasonographic lesions that signify brain injury, and severe ROP were comparable with those reported recently by others.[2-4,9,17] However, the clinical usefulness of these individual risk estimates is limited by their relatively modest predictive accuracy.[18] For example, 53% of infants in our cohort who developed BPD had a favorable 18-month outcome. Conversely, 26% of infants without BPD nevertheless later died or survived with neurosensory impairment. Moreover, many very preterm infants acquire multiple morbidities rather than just a single neonatal morbidity, yet it has remained uncertain whether the associ-

Figure 1. Probability of Poor 18-Month Outcome in Study Infants (N=910) With None, 1, 2, and All 3 Neonatal Morbidities

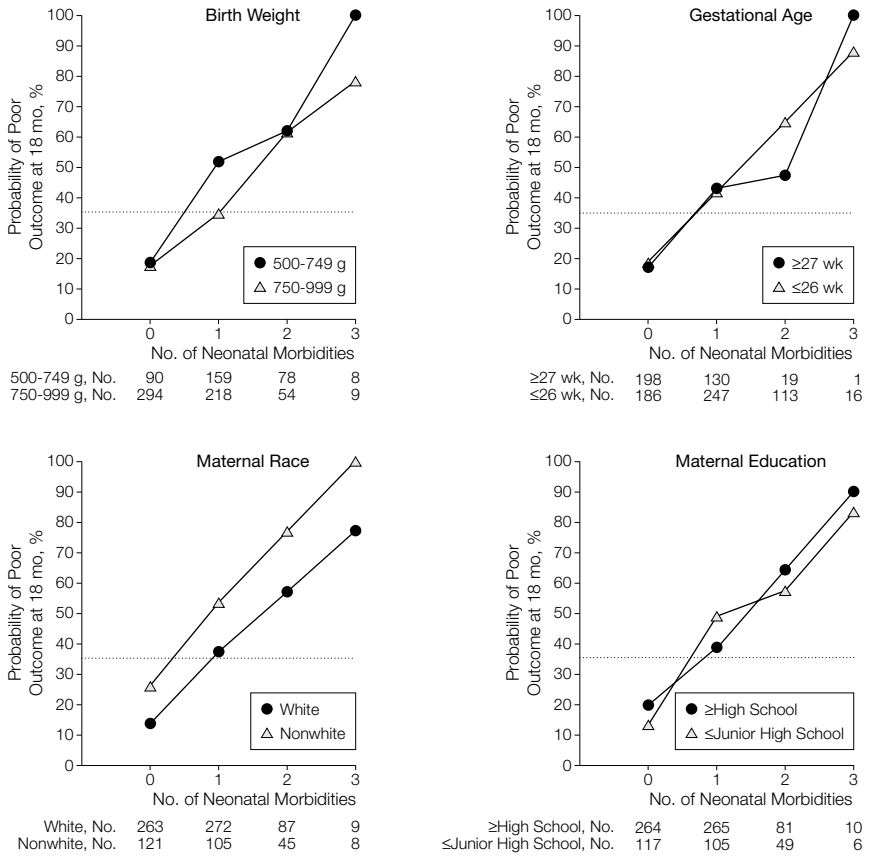


Observed rates of poor 18-month outcome, with 95% confidence intervals (error bars). Solid line indicates predictions based on the fitted morbidity count model; dotted line, the overall probability of a poor 18-month outcome (35%).

ated risks for long-term outcome are independent. We have now shown that they are. Compared with children who have no morbidity, having only 1 of the 3 morbidities approximately doubles the risk of a poor 18-month outcome, while having 2 morbidities approximately triples it.

An obvious question is whether birth weight or gestational age influences the prognostic value of the morbidity count. Not surprisingly, the prevalence of morbidity was higher in the lower birth weight and gestational age strata. For example, only 27% of infants with birth weights of 500 to 749 g remained free of any of the 3 morbidities, compared with 51% of infants with birth weights of 750 to 999 g. However, it is noteworthy that our prediction model applied equally well to both birth weight and both gestational age strata. Importantly, the observed rates of a poor 18-month outcome in children who remained free of all 3 neonatal morbidities were very similar in the 2 subgroups of smaller and bigger infants. This was also true for the 2 subgroups of infants with lower and higher gestational ages. It follows that even very tiny and immature infants have a good probability of a favorable long-term outcome if they survive the immediate neonatal period without serious morbidities. Recently, Doyle and the Victorian Infant Collaborative Study Group[19] reached a similar conclusion. Therefore, although birth weight and gestational age influence the risk of acquiring neonatal morbidities, the latter appear to affect more directly the causal pathways that lead to poor long-term outcome.

Figure 2. Probability of Poor 18-Month Outcome by Morbidity Count, Stratified by Birth Weight, Gestational Age, Maternal Race, and Maternal Education



Observed rates of poor outcome. Dotted lines indicate the overall probability of a poor 18-month outcome (35%).

The morbidity count prediction model also performed equally well in the subgroups of infants born to white and to nonwhite mothers. However, maternal race had an important effect on the observed rates of poor outcome at each of the 4 counts of neonatal morbidities. This effect of race on the prevalence of a poor 18-month outcome is consistent with previous studies that identified maternal race directly[2] or as a component of a social risk score[3] to be a predictor of cognitive outcome at 18 to 20 months in mixed-race populations of ELBW infants. In our study, cognitive delay was most influenced by maternal race, but late death and cerebral palsy were also observed more frequently in children born to nonwhite mothers.

There are several reasons why our inception cohort was especially suited for this study. These strengths include the size and international scope of the cohort as well as the fact that all children were born very recently and during a period of only 2 years. Moreover, all children received prospective standardized assessments, and the loss to follow-up rate at 18 months was very low.

However, it could also be argued that our study sample may not be representative of all ELBW infants who are admitted to a neonatal intensive care unit because our cohort was assembled for a clinical trial. However, both the baseline characteristics at trial entry and the rates of neonatal and 18-month outcomes are comparable with other recent multicenter cohorts of ELBW infants that were not derived from a trial population.[2,20] It is also pertinent that the trial intervention, indomethacin prophylaxis, did not affect the rate of poor outcome at 18 months.[10]

Finally, we need to stress that we did not select our 3 prognostic variables from a larger set. We planned a priori only to examine the prognostic effects of BPD, brain injury, and severe ROP. Therefore, we chose not to split our study cohort into derivation and validation samples. Our results were statistically strong. Nevertheless, the sepa-

rate verification of our prediction model in different populations of ELBW infants would be desirable.

Whenever neurosensory impairment is used to measure the outcome of very preterm infants and the effectiveness of neonatal intensive care, it is necessary to remember that impairment may not be an accurate predictor of functional limitations and disability in later childhood.[21] A child without impairment at 18 months may have learning difficulties at school age, while a child with impairment may function well. Nevertheless, cerebral palsy, cognitive delay, hearing loss, and blindness are important and commonly reported adverse outcomes after very preterm birth.[2,20,22] Parents want to know whether these outcomes are likely to affect their children. Therefore, clinicians need valid evidence that allows them to estimate the risk of impairment with reasonable accuracy. We report that, in ELBW infants who survive to a postmenstrual age of 36 weeks, the prediction of late death or of survival with neurosensory impairment is greatly improved by a simple count of 3 common neonatal morbidities: BPD, brain injury, and severe ROP. This new finding should improve our ability to counsel parents and to anticipate special needs.

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Drafting of the manuscript: Schmidt.
Critical revision of the manuscript for important intellectual content: Schmidt, Asztalos, Roberts, Robertson, Sauve, Whitfield.
Statistical expertise: Roberts.
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