Outcome of respiratory distress syndrome at 28 days: a prospective longitudinal study

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ABSTRACT: Fifty eight newborn infants with respiratory distress syndrome (RDS) were prospectively studied, in order to determine clinical variables prognostic of poor outcome at 28 days.

Twenty six infants survived without bronchopulmonary dysplasia (BPD), 13 had Type 1 BPD, 4 had Type 2 BPD and 15 infants died before 28 days. Survivors without BPD had higher birthweights and gestational ages. Among the other infants, severity of initial lung disease was the best discriminator between outcome groups: Type 1 BPD infants had the best lungs at onset, and the nonsurvivors had the worst lungs. Stepwise multiple logistic regression identified gestational age and the ventilatory index number 1 (VI_1) (=respirator frequency × maximal inspiratory pressure) at day 3 as the most useful variables to predict "poor outcome" (nonsurvival or Type 2 BPD). Ninety five percent of the infants were correctly classified using a cut-off probability of 0.5.

We conclude that RDS outcome at 28 days is determined at a very early stage and that poor outcome can be predicted with reasonable accuracy at three days of age.
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Despite innovative approaches, including maternal treatment with thyroid releasing hormone [1] and neonatal surfactant substitution [2], respiratory distress syndrome (RDS) remains an important cause of neonatal morbidity and mortality. Other interventions will be necessary to further improve RDS outcome once it has developed. Early corticosteroids have recently been reported to decrease the incidence of bronchopulmonary dysplasia (BPD) [3]. Other anti-inflammatory agents may prove beneficial in reducing early alveolar permeability and lung oedema. However, most of the new treatments will carry certain risks. It is, therefore, important to identify, at an early stage, RDS patients with the highest risk for nonsurvival or for serious morbidity. Several scoring systems for RDS severity and the prediction of BPD have been designed. They all appear to have certain limitations: most are retrospective [4–10], some only focus on BPD and do not include nonsurvival as an outcome variable [4–7]. The BPD definition used in most of these studies includes all infants requiring extra oxygen at 28 days [4, 5, 7, 10]. Many of these babies are not seriously ill. In only one study, serious morbidity due to BPD is predicted [6].

In order to address the questions of predicting nonsurvival and severe BPD, we decided to study the outcome of RDS at 28 days in a prospective, longitudinal way. At 28 days, most of the mortality will have occurred and a clinical diagnosis of BPD can be made. We decided to assess BPD severity by using previously described radiological BPD patterns [10–13]: Type 1 is characterized by almost no hyperinflation, with bilateral, ill-defined pulmonary opacities. It is associated with a better prognosis and a very low mortality, in contrast to Type 2. The latter type is characterized by hyperinflated lungs on chest X-ray, with streaky densities interspersed with cystic translucencies. The difference in disease severity has recently been confirmed in a retrospective study of clinical and pathological correlates of the two types: Type 2 BPD had a higher mortality from respiratory causes and was associated with more intensive support from artificial ventilation [14].

Patients and methods

All infants admitted to the Neonatal Intensive Care Unit from January 1 until December 31 1989, and ventilated at day 1 for treatment of RDS, were enrolled in the study. RDS was defined and graded according to clinical and radiological criteria [15]. Patients with lung hypoplasia, according to the radiological criteria described previously [16], were not enrolled. In order to exclude lung infection, an endotracheal aspirate was Gram stained and cultured on admission. Patients with positive endotracheal or blood cultures were excluded.

All infants were ventilated with a time-cycled, pressure-limited ventilator (Bear Cub Infant Ventilator, Bear Medical Systems Inc., Riverside, CA, USA) using a conventional intermittent positive pressure or intermittent mandatory ventilation mode. Ventilator settings aimed at an arterial oxygen tension (Pao_2) of 5.9–11.7 kPa (45–90 mmHg) and an arterial carbon dioxide tension ($Paco_2$) sufficient to maintain pH >7.25. In the year of the study, surfactant was not yet introduced in the unit. Fluid management and therapy for symptomatic ductus arteriosus was according to standard neonatal care [17]. Dexamethasone was used after 10 to 14 days in an attempt to wean infants off the ventilator [18].

The means of the following variables were recorded each day: fractional inspiratory oxygen (Fio_2) as a measure of oxygen exposure, ventilatory index number 1 (VI_1) (=respirator frequency (f) × maximal inspiratory pressure (MIP)) as a measure of exposure to mechanical forces, arterial to alveolar oxygen ratio (a/A ratio=Pao_2/Pao_2) to reflect the degree of ventilation/perfusion mismatch, and ventilator efficiency index (VEI) (=3,800/(f × P × $Paco_2$) where P=MIP - positive end-expiratory pressure (PEEP) measured in mmHg) to reflect the degree of compromise in alveolar ventilation [19].

Presence of unilateral or bilateral crepitations was also recorded daily. Chest X-rays were made on the day of admission and, thereafter, as indicated clinically. Cranial ultrasounds were carried out on clinical indication, and routinely at the end of the first week and before discharge. Intracranial haemorrhages (ICH) were graded I to IV according to PAPILE et al. [20]. Patent ductus arteriosus (PDA) was defined as the presence of clinical symptoms (hyperdynamic precordium, bounding pulses, lung oedema, heart murmur) that prompted institution of medical or surgical therapy. Cardiac ultrasound was available on request but not mandatory for the diagnosis.

At the age of 28 days, four outcome groups were defined: 1) survival without BPD; 2) Type 1 BPD; 3) Type 2 BPD; and 4) nonsurvival. BPD was defined according to BANCALARI et al. [21] as oxygen supplementation, respiratory distress, and an abnormal chest radiograph at 28 days. BPD patients were divided into two groups according to their chest X-ray type at day 28: Type 2, the "classical" BPD X-ray with hyperinflated lung fields and a coarse reticulation characterized by streaky densities interspersed with smaller or larger cystic translucencies; Type 1 with no, or very little hyperinflation and bilateral ill-defined pulmonary opacities spread homogeneously over the lung fields [12, 13]. This classification was made independently by two observers (SVL and HD). After classifying an X-ray as "Type 1" or "Type 2", a radiological Toce score was given in order to correlate a subjective assessment (Type 1 or 2) with a more objective, semi-quantitative assessment [22]. In order to further characterize BPD severity, at day 28, a clinical Toce score was also given [22].

Numerical variables were expressed as medians ±

interquartile ranges. Variables were compared between groups using the Kruskal-Wallis analysis of variance, including multiple comparisons. If only two groups were to be compared, the Mann-Whitney U-test was used. To compare the evolution of ventilatory variables among groups, repeated measurements analysis of variance (ANOVA) was used, including multiple comparisons and analysis for trends. Categorical variables were compared between outcome groups using the Fisher's exact test for m × n tables. Stepwise multiple logistic regression was performed using birthweight, gestational age, Fio_2 and VI_1 at days 1, 2 and 3, and the differences in Fio_2 and VI_1 between days 1 and 3, to determine variables that predict "poor outcome" (nonsurvival or Type 2 BPD) at 28 days. A significance level of 0.05 was used to include, and of 0.1 to remove variables. The cut-off probability used in the classification table to predict "poor outcome" was 0.5.

Results

Because of RDS, 58 infants were ventilated at day 1. They had a median gestational age of 29 weeks [interquartile range 28–30 weeks], (range 24–38 weeks) and a birthweight of 1,335 g [948–1,453 g], (range 540–2,900g). Twenty six infants survived without BPD, 13 developed Type 1 BPD, 4 developed Type 2 BPD and 15 newborns did not survive beyond 28 days.

Initial characteristics of the study groups

Initial characteristics of the study groups are presented in table 1. There was a striking difference in birthweight and gestational age between groups: survivors without BPD had a higher birthweight (p<0.01) and gestational age (p<0.05) than Type 1 BPD, Type 2 BPD and nonsurvivor groups. There was no difference in birthweight or in gestational age between the latter three outcome groups.

Sex, Apgar scores and radiological RDS grades did not distinguish between groups.

The severity of initial lung disease, expressed as the a/A ratio and the VEI at days 1 and 2, discriminated between survivors without BPD or Type 1 BPD, and nonsurvivors (p<0.01). Type 2 BPD patients had intermediate values.

Respiratory characteristics during the first four weeks

Oxygen requirements. The evolution of Fio_2 during the first four weeks showed a significant intergroup difference (fig. 1). Nonsurvivors had higher oxygen needs throughout their course than survivors without BPD or with Type 1 BPD. Type 2 BPD patients had immediate oxygen requirements for the first six days, and higher Fio_2 values than survivors without BPD thereafter.

Table 1. — Characteristics of the study groups at the onset

	No BPD	Type 1 BPD	Type 2 BPD	Nonsurvival
n	26	13	4	15
Birthweight g	1825 ** [1475–2085]	980 [835–1360]	840 [580–1190]	1000 [870–1370]
Gestational age weeks	32 * [30.5–33.5]	28 [27–29]	28.5 [26–29]	28 [27–29]
Sex M/F	16/10	7/6	1/3	12/3
Apgar score				
1 min	6 [3–8]	5.5 [1.25–7]	3 [3–4]	4 [2–6]
5 min	9 [7.25–9]	9 [8–9]	7.5 [7–8]	7.5 [6.75–9.25]
Radiological RDS grade n				
I/II	13	6	0	6
III/IV	13	7	4	7
Pao_2/Pao_2 ratio				
day 1	0.16 [0.13–0.22]	0.14 [0.11–0.31]	0.13 [0.09–0.16]	0.08† [0.05–0.09]
day 2	0.23 [0.13–0.32]	0.21 0.12–0.30]	0.11 [0.08–0.17]	0.07† [0.06–0.09]
Ventilatory efficiency index min·mmHg^{-2}				
day 1	0.13 [0.06–0.16]	0.07 [0.06–0.11]	0.08 [0.05–0.12]	0.03†† [0.02–0.05]
day 2	0.15 [0.06–0.30]	0.07 [0.05–0.11]	0.06 [0.03–0.08]	0.03† [0.02–0.03]

All variables are expressed as medians [interquartile ranges] unless otherwise stated. *,**: $p<0.05$, $p<0.01$, respectively, compared to other 3 groups, by Kruskal-Wallis ANOVA; †: $p<0.01$ compared to No BPD and Type 1 BPD groups, by Kruskal-Wallis ANOVA; ††: $p<0.01$ compared to No BPD groups; $p<0.05$ compared to Type 1 and Type 2 BPD groups, by Kruskal-Wallis ANOVA. Pao_2: arterial oxygen tension; Pao_2: alveolar oxygen tension; BPD: bronchopulmonary dysplasia; RDS: respiratory distress syndrome.
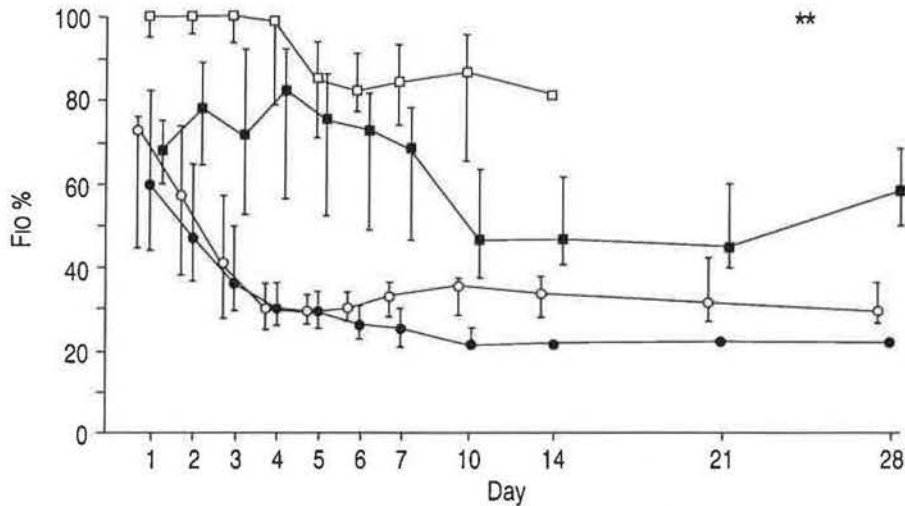

Fig. 1. — Fractional inspiratory oxygen (Fio_2) of the study groups during the course of respiratory distress syndrome (RDS). Fio_2 at each day is expressed as median (interquartile range as bars) for each outcome group. **: $p<0.01$ for global analysis with repeated measurements analysis of variance (ANOVA). This means that the overall course of Fio_2 over the 28 day period is different for each group. ●: survivors without BPD; O: Type 1 BPD; ■: Type 2 BPD; □: nonsurvivors; BPD bronchopulmonary dysplasia.

Infants without BPD or with Type 1 BPD showed a decrease in oxygen needs from day 1 to day 3, whereas nonsurvivors and Type 2 BPD patients showed none. Finally, despite similar oxygen requirements during the first week, Type 1 BPD patients continued to require extra oxygen thereafter, unlike their non-BPD counterparts who showed a further decrease in Fio_2 from day 5 to 10 ($p<0.05$).

Ventilatory assistance

Similarly, the evolution of VI_1 during the first four weeks was different for the four outcome groups (fig. 2). Nonsurvivors had a higher VI_1 than survivors without BPD or with Type 1 BPD throughout their course. Type 2 BPD patients had intermediate values for the first 3 days, but from day 4, they had persistently higher values than patients without BPD. After 10 days, Type 2 BPD patients also had higher VI_1 values than their Type 1 counterparts. From day 1 to day 3, survivors without BPD and Type 1 BPD patients showed a significant decrease in ventilatory support, whereas this was not the case in the two "poor outcome" groups (p<0.05).

Severe ICH (Grades III and IV) was more frequent in nonsurvivors compared to survivors (p<0.01). Nonsurvivors and type 2 BPD infants had more air leaks than others (p<0.01). They also had a higher incidence of PDA (p<0.01).

Clinical BPD scores according to Toce were higher in the Type 2 BPD group as compared to the Type 1 group: 13 [10–15] *versus* 7 [4–8] (p<0.01). The same was true for the radiological Toce scores: 6 [4–7] *versus* 2 [2–3] (p<0.01).

After 28 days, there was one death in a Type 2 BPD patient (at day 42, whilst on the ventilator). In the 16 remaining BPD patients, the duration of artificial ventilation was longer for Type 2 than for type 1 patients: 31 [18–51] days *versus* 6 [6–11] days
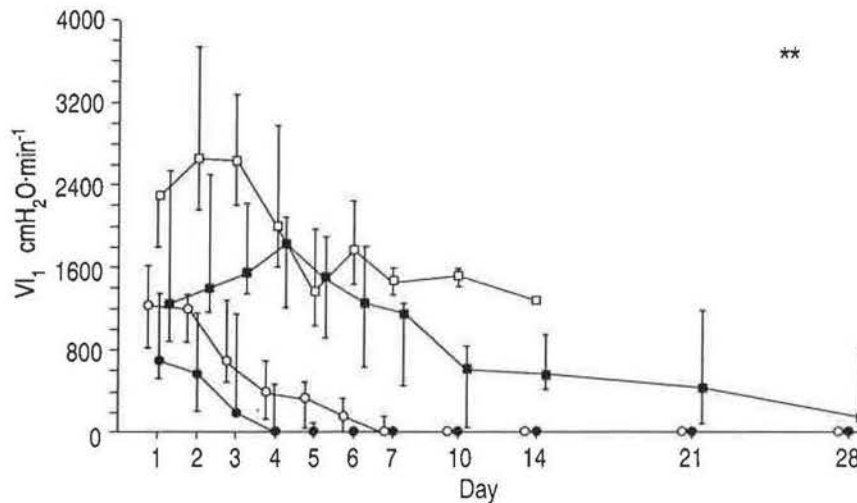

Fig. 2. – Ventilatory index 1 (VI_1) of the study groups during the course of respiratory distress syndrome (RDS). VI_1 at each day is expressed as median [interquartile range as bars] for each outcome group. **: p<0.01, for global analysis with repeated measurements analysis of variance (ANOVA). This means that the overall course of VI_1 over the 28 day period is different for each group. ●: survivors without BPD; O: Type 1 BPD; ■: Type 2 BPD; □: nonsurvivors; BPD: bronchopulmonary dysplasia.

Chest auscultation revealed uni- or bilateral crepitations in the majority of patients at day one. After five days, the crepitations had disappeared in almost all survivors without BPD; only three of them had occasional unilateral rales. In the three other groups, uni- and bilateral crepitations persisted throughout the disease course in more than half of the infants. The chest auscultation did not discriminate between both BPD groups and the nonsurvivors.

Outcome at 28 days

Causes of death in the nonsurvivor group were respiratory failure with intracranial haemorrhage (8 patients), respiratory failure due to RDS (4 patients), and multiple organ failure (3 patients). In all cases death occurred despite maximal supportive therapy. Without exception, histopathological examination of the lungs revealed BPD lesions in varying stages of evolution, but always with prominent airway lesions (bronchiolar mucosal erosions, metaplasia and bronchiolitis obliterans) and some degree of interstitial or alveolar emphysema and interstitial fibrosis.

(p<0.01). The duration of oxygen dependency was also longer for Type 2 than for Type 1 infants: 695 [103–791] days *versus* 66 [42–83] days (p<0.05).

Predictive features

Gestational age and VI_1 at day 3 were selected with coefficients of -0.993 (relative risk 0.370, 95% confidence limits 0.124–1.110) and 0.004 (relative risk 1.004, 95% confidence limits 1.001–1.007), respectively. The intercept was 21.860. With a cut-off probability for "poor outcome" at 0.5, 95% of the patients were classified correctly (sensitivity 88%, specificity 97%, false positives 7%, false negatives 5%).

Discussion

We preferred to include nonsurvivors in the "poor outcome" analysis, unlike other authors who only consider BPD and make abstraction of nonsurvivors

[4–7]. Omitting nonsurvivors is inappropriate if one wants to develop predictive variables that can be applied prospectively. It can be argued that a number of deaths are due to nonrespiratory causes and that these infants would be inappropriately enrolled in trials, aimed at improving RDS, if the predictive variables of our study are used. However, in our study population, all 15 infants who died showed histopathological signs of severe RDS, including major airway lesions, which have been correlated with Type 2 BPD [14]. Their initial RDS severity was worse than that of any other group, and their oxygen and artificial ventilation requirements were the highest. This suggests that, in infants ventilated for RDS, nonsurvival is almost always associated with severe lung disease, and that combining nonsurvival with Type 2 BPD in outcome analysis is justified.

Scoring BPD severity by its radiological type was chosen because different authors had published and validated this scoring system [11–14]. Moreover, it was easy to use according to our own clinical experience. Although it is a qualitative assessment, there was a clearcut difference in radiological Toce scores between the two types: all Type 2 X-rays had a score below 4. All Type 1 radiographs scored 4 or more. This guarantees a reasonable degree of objectivity and consistency in assigning a BPD type at day 28.

The results of this study show that it is possible to predict "poor outcome" (nonsurvival or Type 2 BPD) of RDS at a very early stage, using the combination of gestational age and VI_1 at day 3. It is not surprising that the degree of prematurity and the severity of early lung disease were identified as best predictors. Previous studies have shown correlations between gestational age and the incidence of death and BPD [4, 23, 24]. Correlations with the severity of initial lung disease have also been made [4, 10, 25, 26]. It is promising that the prediction of 28 day outcome was already possible at day 3, with 95% of the infants classified correctly. This offers the possibility of directing new therapies only at the very high risk patients, at a time when irreversible damage might still be prevented.

It is interesting to note, that survivors without BPD and type 1 BPD infants had similar and decreasing oxygen requirements during the first week, but diverged thereafter, with the "Type 1" infants maintaining slightly higher oxygen needs and failing to be weaned down further. On the other hand, the latter group had a worse VEI and a higher VI_1 at the onset. This was exclusively due to a higher ventilator frequency (data not shown), suggesting a high deadspace/alveolar volume ratio due to alveolar microatelectasis. It may be hypothesized that Type 1 infants begin to suffer from oxygen toxicity after 7 days, as opposed to the non-BPD babies who are more mature and have better defences against oxygen toxicity [27]. Additionally, the more aggressive ventilation from the start could be a contributing factor.

Similarly, it was interesting to note that crepitations persisted throughout the 28 day course in BPD patients. Crepitations are thought to be the result of pulmonary oedema caused by surfactant deficiency and increased pulmonary epithelial permeability. Resolution of RDS coincides with normalization of epithelial permeability; in infants who develop BPD, pulmonary permeability fails to return to normal [28]. This probably explains the persistence of crepitations beyond five days in future BPD patients.

We acknowledge that this study was conducted in the pre-surfactant era. It is possible that - with surfactant - the incidence of severe lung disease and the number of deaths would be less [2]. However, it seems likely that infants who - despite surfactant replacement therapy - would fall into our "poor prognosis" group at day 3, are indeed at high risk for nonsurvival or Type 2 BPD.

Finally, this study looked at short-term outcome of infants, ventilated for RDS. We are at present conducting a follow-up study of these infants in order to determine the long-term outcome.

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