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Impact of Chronic Lung Disease on Very Low Birth Weight infants: a collaborative study of the Italian Group of Neonatal Pneumology

Incidenza della malattia polmonare cronica nei neonati di peso < 1500 g: uno studio multicentrico del Gruppo Italiano di Pneumologia Neonatale

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Summary

Objective. To evaluate the incidence and risk factors for chronic lung disease in a population of very low birth weight infants.
Methods. In a prospective multicentric trial all very low birth weight infants (< 1500 g) accepted in 36 Italian Neonatal Intensive care units were studied from February 89 to January 99. For each patient were recorded maternal history, perinatal events, respiratory disease, infections, patent ductus arteriosus, retinopathy of prematurity, intraventricular haemorrhage and final outcome. Logistic regression analysis was performed in a multivariate assessment of risk factors for chronic lung disease.
Results. In the study were included 1634 patients: 1387 infants survived beyond 36 weeks and 6.9% of them still oxygen dependent.
The incidence of chronic lung disease was higher among babies with a gestational age of < 28 weeks and weight ≤ 1000 g. The multivariate analysis showed that low birth weight, respiratory distress syndrome, persistent ductus arteriosus and sepsis were the main risk factors.
Conclusions. In our study the incidence of chronic lung disease was relatively low

Key words

Neonatal intensive care unit • Very low birth weight • Chronic lung disease • Neonatal sepsis • Collaborative research

Parole chiave

Terapia intensiva neonatale • VLBW • CLD • Sepsi neonatale • Studio multicentrico

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Riassunto

Obiettivo. *Valutare l'incidenza ed i fattori di rischio per malattia polmonare cronica in una popolazione di neonati con peso alla nascita < 1500 g.*
Materiali e metodi. *In uno studio prospettico multicentrico sono stati considerati tutti i pazienti con peso < 1500 g ricoverati presso 36 Terapie Intensive Neonatali tra Febbraio 1998 e Gennaio 1999; per ogni paziente erano riferiti i dati perinatali, l'anamnesi ostetrica, la patologia respiratoria, la presenza di complicanze cliniche e la prognosi. È stata eseguita un'analisi di regressione logistica per valutare i fattori predittivi la malattia polmonare cronica.*
Risultati. *Sono stati studiati complessivamente 1634 pazienti: 1387 pazienti sopravvivevano oltre le 36 settimane di età gestazionale ed il 6,9% di questi sviluppava una malat-*

tia polmonare cronica. I pazienti di età gestazionale < 28 e peso ≤ 1000 g ne erano più frequentemente affetti.
Risultano fattori di rischio per malattia polmonare cronica: il basso peso, la malattia delle membrane ialine, il dotto di Botallo pervio e la sepsi.
Conclusione. *L'incidenza della malattia polmonare cronica è risultata modesta: ciò è probabilmente imputabile all'esigua percentuale di soggetti con peso ed età gestazionale estremamente bassi inclusi nello studio ed alla loro elevata mortalità prima delle 36 settimane post-concezionali. I dati sono inoltre difficilmente confrontabili con i lavori pubblicati per i diversi "target di ossigenazione" valutati, per l'eterogeneità dei pesi e per le differenti definizioni di malattia polmonare cronica adottate.*

Introduction

CLD (Chronic lung Disease) is one of the most difficult complications of prematurity: surfactant and the continuous development of less aggressive ventilatory techniques has recently improved the course of the disease but not the percentage of affected infants [1-3].
The incidence of CLD is increasing together with the increment of ELBW (extremely low birth weight) babies, as the more premature they are the longer is their oxygen dependency [4].
The sudden interruption of pulmonary development induced by premature delivery plays a crucial role in the pathogenesis of the disease [5], which could be in part worsened by repeated courses of prenatal steroids. If on the one hand these drugs are known to enhance lung maturity and improve infant survival, on the other hand they interfere negatively with early pulmonary and brain development [6-8].
Immediately after birth, other risk factors – mainly depending on each NICU's (Neonatal Intensive Care Unit) management of ventilation, nutrition, fluid intakes, etc. – interfere with the occurrence of various degrees of CLD.
Like other worldwide initiatives [9-17], the Italian Neonatal Pneumology Group comprises a volunteer group of NICUs established to perform collaborative clinical research in this field. The aim of the study was to evaluate the incidence of CLD among a population of VLBW infants in Italy and to estimate the degree of association between CLD and some of the clinical variables potentially related to the event.

Patients and methods

The network for the study on CLD comprised 38 NICUs from twelve different Italian regions (23 in the North, 5 in the Centre, 10 in the South).
The study population included all VLBW infants admitted to the 38 NICUs during 12 consecutive months (February 1998-January 1999): 8 NICUs were in University hospitals and 30 in General hospitals. The survey was conducted by the same individual(s)/doctor(s) within each unit for the entire study period, using pretested standardised data form and instructions previously set up by all participants. The Co-ordinating Centre reviewed the completed forms to ensure completion and internal consistency. A computer programme was employed to validate the intrinsic consistency of the data through crosschecks of dates, diagnoses and management.
Clinical information recorded for each infant was as follows:

- name, date, place of birth, GA (gestational age) (calculated by ultrasound scan or Dubowitz assessment);
- SGA (small for gestational age), defined as birth weight below the 10th percentile for each GA and adjusted for sex according to national growth charts [18];
- maternal pre-eclampsia, defined as the presence of hypertension and proteinuria;
- PPROM (preterm premature rupture of the membranes), if rupture occurred 24 hours before delivery;
- prenatal infections were diagnosed in the presence of maternal fever with leucocytosis during labour and positive vaginal swabs;
- antenatal steroid therapy, defined as maternal bethametasone therapy – was considered completed only after two doses of betamethasone (12 mg/day) 24 hours before delivery;
- CRIB score was used to assess the clinical severity of infants admitted to the NICU [19];
- RDS (Respiratory Distress Syndrome) was diagnosed from standard clinical signs and chest X-rays [20];
- type and duration of IPPV (Intermittent Positive Pressure ventilation) and HFOV (High frequency Oscillatory ventilation), alone or combined, were recorded;
- CPAP (Continuous Positive Pressure) referred only to NCPAP (Nasal Continuous Positive Pressure) therapy used without previous mechanical ventilation;
- Surfactant (CUROSURF®) therapy, doses and time of administration were recorded;
- CLD, the primary outcome of the study, was defined as being oxygen dependent at 28 days of life and receiving supplemental oxygen at 36 weeks of corrected age to maintain SaO2 ≥ 92%;
- PDA (Patent Ductus Arteriosus) diagnosed by typical clinical, radiological and echocardiographic findings, was considered when receiving pharmacological treatment to facilitate ductal closure or surgical legation;

- Sepsis was defined in the presence of positive blood cultures or clinical signs of deterioration due to generalized infection plus significant laboratory studies (anomalies of white cell count and I/T neutrophil ratio, increase in C reactive protein);
- NEC (Necrotizing enterocolitis) was diagnosed, according to the criteria of Bell et al. [21], if there was blood in the stools and pneumatosis intestinalis on abdominal X-rays;
- IVH (Intraventricular haemorrhage) diagnosed by serial ultrasound scans of the brain was classified according to Volpe [22] and taken into consideration if > II;
- ROP (Retinopathy of Prematurity) was evaluated using the International Classification of Retinopathy in Prematurity [23] and taken into consideration if > II;
- Major (life-threatening) malformations were diagnosed by clinical signs or instrumentally.

Data analysis

Data management and analyses were carried out using the EPI6 software package (Centres for Disease Control and Prevention, Atlanta; GA).
Continuous measures were compared using t-test, whereas quantitative estimates of the effects of various covariates such as demographic variables and pathological events were obtained using OR and 95% CI. The test of statistical significance for contingency tables was based on the usual χ^2 value comparing the observed and expected numbers of events. Where appropriate, potential confounding effects were controlled by stratification and the Mantel-Haenzel procedure.
Logistic regression analysis was performed for the primary outcome measure (CLD) to determine which were the statistically significant predictors of the disease, using SAS statistical software on a 6410 VAX computer. The stepwise selection procedure was used to define the best model fitting the data, including variables for which the p-value was less than 0.25. All tests were considered statistically significant at a value of $p < 0.05$.

Results

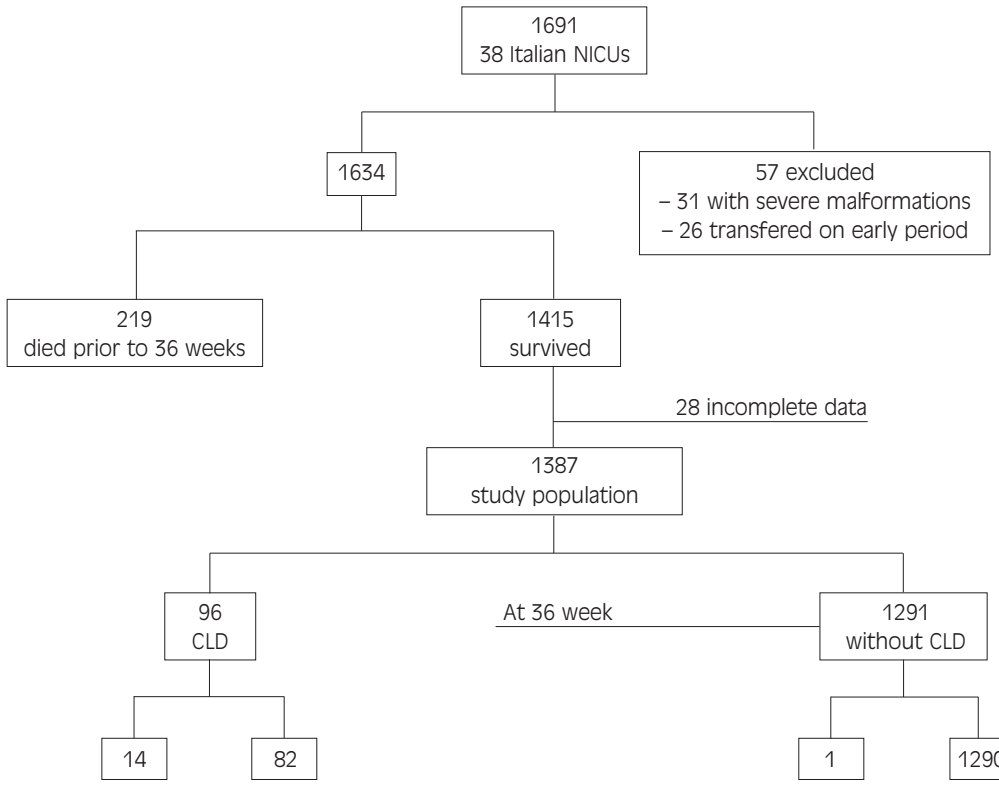
A total of 1691 live infants weighing ≤ 1,500 g were admitted to the 38 NICUs during the one-year study period (Tab. I). Each centre treated between 16 and 99 VLBW infants, with a median of 58 infants. Mean birth-weight of 1,634 infants was 1123 ± 277 g, while mean GA was 29.6 ± 3.0 weeks. The overall mortality was 14.3% (234/1634) and among the babies weighing ≤ 1,000 g and ≤ 750 g it was respectively 37% (199/537) and 56% (122/218).
A total of 96 (5.8%) babies met the definition of CLD; the incidence of CLD among VLBW infants surviving at 36 weeks of GA was 6.9% but 19.2% of the whole study population died or was oxygen-dependent at 36 weeks of corrected age (Fig. 1). The 1387 infants surviving beyond 36 weeks of corrected age, constituted the study population; the demographic variables and the clinical conditions of the infants by CLD presence are shown in Table II. Among this cohort of 1,387 VLBW infants, CLD babies had lower birth weight and GA, and there was no significant difference if they were growth retarded foetuses (32.3% *vs.* 30.9%); males were 59.4% and a high percentage of both groups were inborn. The incidence of maternal preeclampsia and PPROM was not remarkable. As many as 71.9% of babies with CLD were born by Caesarean section, while multiple deliveries were more often in the group of the non-oxygen dependent infants. Maternal fever and positive vaginal swabs were not considered because of data inconsistency. Antenatal steroids were given to the CLD group in 59.4% *vs.* 55.4% of the comparison group. In the CLD group CRIB score was much higher (p-value 0.0000) than the Apgar score.
The bivariate analysis of illness, postnatal interventions and clinical complications according to the presence of CLD are shown in Table II.
RDS was the main respiratory illness and was of course prevalent among CLD babies; as a consequence, surfactant therapy was performed in 82.3% of babies with CLD *vs.* 36.3% of the others. Mechanical ventilation was needed in 100% *vs.* 44.6%. Mean ventilation time of the CLD infants was 27.5 days (range 0.6-101) against only 2.73 days (range 0.04-30) in the non CLD group. None of the affected babies was treated exclusively with NCPAP, while 281/1291 (21.7%) of the

Tab. I. General data of VLBWi.

VLBWi (n)	1691 (1634)
Birth weight(g)	1123 ± 277
Gestational age (w)	29.6 ± 3
SGA	29.9%
Female	52.2%
Inborn	81%
Caesarean delivery	76.3%
Apgar score 1 minute ≤ 3	26.8%
Apgar score 5 minute ≤ 5	9.9%
CRIB SCORE	3.5 ± 4,2
Antenatal steroids	52%
Multiple gestation	15.65
Placenta previa	3.7%
Preeclampsia	19.2%
HELP syndrome	3%
Chorionamnionitis	1.2%
PPROM	15%
Oligoanidramnios	3.9%
Positive vaginal swabs	Incomplited data
Fever during labour	Incomplited data
Maternal leucocytosis	Incomplited data
Fetal distress	11.6%
Fetal growth retardation	26%

Data are reported as mean (± SD)

Fig. 1. Distribution of study population (VLBW i ≤ 1,500 g).



comparison group did not need to be intubated and were on NCPAP for a short period of time. HFO as first intention was very seldom utilised, (only 14 infants). HFO as a rescue therapy was performed in 83 patients, 53 of whom (63.8%) did not develop CLD. Postnatal steroids were used in 67.7% of CLD *vs.* 13.6% of the comparison group. The overall incidence of complications was much higher in the oxygen dependent group. PDA required pharmacological treatment or surgical legation in 46.9% of the affected babies *vs.* 14.1% of the others (p = 0.0000), sepsis occurred in 65.6% of CLD babies *vs.* 15.0% (p = 0.0000), IVH > II was 26% *vs.* 7.4% (p = 0.0000), and ROP was 21.8% *vs.* 1.2% (p = 0.0000). NEC 8.3% *vs.* 3.2% (p = 0.0081). Deaths after 36 weeks corrected age occurred mainly in the group of affected babies (14/96 *vs.* 1/1291; p = 0.0000). Hospitalisation time was almost double if compared to the control group 119.9 ± 72.8 days in the CLD group *vs.* 56.3 ± 28.5 days in the comparison group (p = 0.0000).

The analysis of the data demonstrated that CLD occurs more frequently in babies < 28 GA (21.5% *vs.* 4.2%) and ≤ 1000 g of BW (19.8% *vs.* 2.76%) The percentage of patients with CLD according to GA and BW is shown in Figure 2. In particular, 50% of the infants ≤ 25 weeks GA and weighing < 750 g were CLD, while the percentage was 32% if their weight was between 751 and 1,000 g. The incidence of CLD among infants born at 26-27 weeks GA weighing < 750 g was 37% but if their weight was comprised between 751 and 1,000 g the percentage dropped to 12.3%. Babies of older GA (≥ 28) are prone to the disease especially when they are growth retarded and usually when their birth weight is below 1,000 g (13.4% *vs.* 2.6%).

The multivariate analysis predicting CLD (Tab. III) per 100 g of weight decrement shows that, besides low birth weight (OR 1.62 -CI: 1.44-1.83) and RDS (OR 6.58- CI: 2.82-15.40), PDA and sepsis were the main risk factors with an OR respectively of 2.82 (CI: 1.57-5.17) and 3.01 (CI: 1.97-4.59).

Discussion

CLD is a typical lung disease affecting babies born very prematurely, less than 28 weeks GA, weighing less than 1,000 g and more frequently males [24-26]. To these risk factors already well known in the literature, there are some others mainly due to the long periods of care in NICU: they include the need for prolonged mechanical ventilation that leads to inflammatory cascade, the development of sepsis and often patency of the ductus arteriosus [27-29].

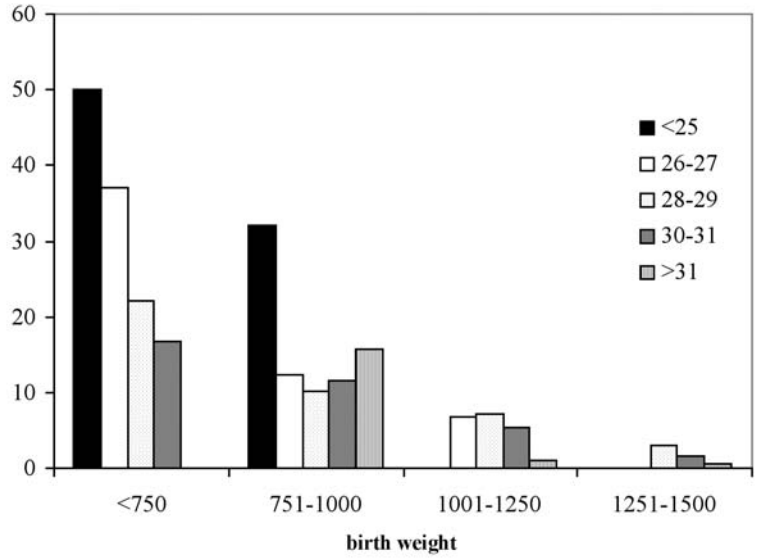
The occurrence of CLD therefore seems to be more related to later events than to the initial respiratory disease [30]. In our study population the group of ELBW

Tab. II. Bivariate analysis of demographic, prenatal and perinatal characteristics, illness, postnatal interventions and clinical complications according to the presence of CLD.

	CLD (n = 96)	No CLD (n = 1291)	p-value
Birth weight (g)	899 (± 255.7)	1199 (± 226.1)	0.0000
Gestational age (wk)	27.7 (± 2.5)	30.4 (± 2.6)	0.0000
Small for Gestational Age	31 (32.3%)	399 (30.9%)	0.7771
Gender (% male)	57 (59.4%)	594 (46.1%)	0.0118
Inborn (%)	80 (83.3%)	1063 (82.3%)	0.8051
Maternal pre-eclampsia	17 (17.7%)	288 (22.5%)	0.2773
Antenatal Steroids (%)	57 (59.4%)	713 (55.4%)	0.4495
PROM (%)	15 (15.6%)	186 (14.4%)	0.7484
Caesarean section	69 (71.9%)	1047 (81.1%)	0.0278
Multiple delivery	12 (12.5%)	241 (18.7%)	0.1311
Apgar score ≤ 3 at 1 min	1.7 (± 0.9)	2.1 (± 0.9)	0.0379
< 6 at 5 min	2.1 (± 0.9)	4.1 (± 1.3)	0.7213
CRIB score	6.2 (± 3.7)	2.3 (± 2.6)	0.0000
RDS (%)	93 (96.9%)	844 (68.5%)	0.0000
VMC (%)	100 (100%)	575 (44.6%)	0.0000
Surfactant (%)	69 (82.3%)	393 (36.3%)	0.0000
Postnatal steroids (%)	65 (67.7%)	175 (13.6%)	0.0000
PDA (%)	45 (46.9%)	182 (14.1%)	0.0000
NEC (%)	8 (8.3%)	41 (3.2%)	0.0081
IVH > II (%)	25 (26%)	93 (7.4%)	0.0000
SEPSIS (%)	63 (65.6%)	194 (15.0%)	0.0000
ROP	21 (21.8%)	15 (1.2%)	0.0000
Deaths (n)	14 (14.6%)	1 (0.08%)	0.0000
Length of hospitalisation (days)	119.9 (± 72.8)	56.3 (± 28.5)	0.0000

Mean (± SD)

Fig. 2. Percentage of patients with CLD according to gestational age and birth weight.



represented 33% of the whole sample; outborns were only 19%, probably because in our country deliveries at high risk are performed in 3rd level centres, particularly in the north, with a high-density population and with many NICUs close to one another. The use of antenatal steroids reached an average of 52% (min 27%

Tab. III. Multivariate analysis predicting CLD (n = 1387 VLBW infants).

Factor	OR-crude	_i	OR-adjusted	C.I. (95%)	p-value
Birth weight, per 100 g decrease		0.06	1.62	1.44-1.83	0.0000
Gender (male vs. female)	1.77	0.28	1.95	1.12-3.39	0.0187
RDS	21.73	0.43	6.58	2.81-15.40	0.0000
PDAT	7.40	0.30	2.82	1.57-5.17	0.0005
VMC	9.20	0.35	2.29	1.16-4.53	0.0176
SEPSIS		0.22	3.01	1.97-4.59	0.0000

Likelihood Ratio = 282.1002 d.f. = 6; p-value = 0.0000

max 75%) and it was 59% in the CLD group. This observation simply indicates that prophylaxis is more common in high-risk pregnancies. From the literature it seems that their beneficial effect on the lungs does not alter the overall incidence of CLD; the administration of lung surfactant to a wide number of patients and the less aggressive ventilation now adopted in many intensive care units, could mask the positive impact of antenatal steroids. This hypothesis is supported, according to some authors, by the enhanced number of survivors between the VLBW infants, compared to a concomitant lack of decline in the CLD group [31 32].

Twin pregnancies and PPROM did not interfere significantly with the incidence of CLD (Tab. I). Prenatal infections diagnosed by the occurrence of maternal fever, leucocytosis 24 hours before delivery and positive vaginal swabs, all well known high risk factors for the development of chronic lung disease were unfortunately underestimated in our study. This was due to a lack of data transmission between the obstetric and the neonatologic teams. Chorioamnionitis is known to enhance lung maturation, but at the same time it is responsible for the onset of severe lung inflammation that predisposes to the occurrence of chronic lung damage [33-35]. SGA infants represented almost 30% of our study population and the percentage of those who developed CLD did not differ significantly from the non CLD group; stratifying for birth weight we were able to observe that the babies affected by CLD mostly weighed less that 1,000 g, implying that infants born over 28 weeks GA were prone to the disease mainly if they were growth restricted (Fig. 2). This observation is in accord with that of Tyson who noticed that nowadays there is a higher survival rate of intra uterine growth retarded foetuses, born more prematurely and more often affected by chronic lung disease. This data is evident if a special subgroup is considered, i.e., those weighing < 1,000 g born from mothers with pre-eclampsia [36].

The CRIB score was significantly higher in CLD babies, reflecting a worse clinical condition in the first 12 hours of life and the use of high FiO2 at birth. Average time of hospitalisation was almost double for babies affected by CLD; there is an association between length of hospital stay, low birth weight and low gestational age although – excluding birth weight and gestational age – CLD is surely responsible for increasing hospitalisation time in these newborns [37]. Exogenous surfactant was administered to 82% of the CLD group and to 17.7% of the comparison group as a result of the different degree of respiratory distress or immaturity in the two groups.

According to the literature the real impact of CLD among very low birth weight infants is difficult to be defined. The lack of uniformity in the diagnostic criteria of CLD is responsible for much of the variations in incidence of the disease between different authors. Bancalari shows a strikingly different incidence in CLD among premature infants, according to various definitions (5.9% if oxygen is administered during the first 28 days of life, 47.1% if oxygen is administered for ≥ 28 days during hospitalisation, 25% if oxygen is administered at 36 weeks CA); that is why CLD in the VLBW newborns, as reported by the recent literature, ranges between 4% to 35% [3]. In our study CLD at 36 weeks GA occurred in only 5.8% of the whole population with an overall mortality rate of 13.4% before 36 weeks CA. Surely the incidence of mortality for this population influences the incidence of the pathology itself; as a matter of fact in our study, analysing the combined outcome of CLD + death, the percentage rises to 19.2%.

Obstetric management in the delivery room, resuscitation at birth, mechanical ventilation, with the vast variety of different ventilators and ventilating strategies could be some of the reasons why the results of the outcome CLD can be so different [38-43].

In Northern Europe, where VLBW infants are mainly assisted by NCPAP, instead of IPPV, the percentage of babies with CLD is relatively lower: 12.8% in Norway [10], 13% in Finland [13], 14% in Sweden [12]. This data is not only due to ethnic differences or social problems, but also probably to more gentle ventilation with a less aggressive approach to the patient, starting from the delivery room. Van Marter compared two Intensive Care Units with the same mortality rate and found marked differences for what concerns the incidence of CLD. In Boston it is 22% while at the "Babies" in N.Y. City it is 4%. The smooth resuscitation at birth and the wider and more precocious use of NCPAP in the second Unit is

thought to be the main factor determining the different pulmonary outcome [44].

The National Italian trial conducted by Rubaltelli [45] in 1998 reports a 5.6% of babies O_2 dependent at 28 days of life, but referred to a population of neonates affected by RDS and not only VLBW infants; this data cannot be compared with ours as CLD was defined with different criteria. We observed that the incidence of CLD was significantly higher in the neonates ≤ 1,000 g or < 28 weeks gestational age. In our study, the babies admitted to the 38 NICUs had similar demographic factors and among them there was a relatively low number of very high-risk neonates, weighing less than 1,000 g (537/1,634) with a high mortality rate of 37%; we presume that this could have interfered with the incidence of CLD in our population.

All CLD babies were intubated, while only 38.6% of the non CLD group underwent artificial ventilation, confirming the role of artificial ventilation in enhancing the inflammatory cascade that leads to lung damage. Of our population 67.7% received postnatal steroid therapy in order to reduce the time of ventilation, but sometimes this therapy was also prescribed to reduce oxygen dependency after extubation. In the future the restriction of this treatment to the most severe cases will be of the utmost importance to avoid the risk of worsening a baby's neurological outcome [46 47].

Different authors observed that oxygen dependency at 36 weeks' corrected age was not mainly related to perinatal factors, but was more likely due to difference in practice style among NICU's and to complications occurring later in the first weeks of life [48]. In our study patients were treated according to the different clinical practice of each NICU, and the level of oxygenation considered acceptable by the different clinicians was not standardized.

Mild forms of CLD tend to become more severe if clinical complications occur, mainly in the subgroup of babies born with extremely low birth weights. In our study the incidence of ROP, PDA, IVH, NEC and sepsis was much higher in the CLD group. Sepsis was the more frequent complication occurring in 25% of our babies with CLD, similar to the 21% found in other studies [26].

The multivariate analysis, stratified by 100 g of weight, predicting CLD shows that the lowest weights, together with the presence of RDS, the persistence of PDA and the onset of sepsis are the prevalent risk factors. Once again, as other authors observed, we found that CLD is related not only to the initial respiratory distress but particularly to the presence of later clinical complications.

Conclusions

The incidence of CLD is highly influenced by the different definitions adopted for the disease and by the different levels of "oxygenation targets" in various NICUs around the world. The result CLD + death seems to be a more reliable outcome. Our data show that a relatively small number, 6.9% of the VLBW infants studied, were diagnosed as CLD, but this percent rose to 19.2% if CLD + death was considered as outcome. A more careful resuscitation in the delivery room and a better choice of ventilatory techniques, in the future, will hopefully reduce the total number of CLD babies. However, the more severe forms of chronic lung disease, with poor prognosis "quoad valetudinem", will only diminish along with a reduction in clinical complications. Nosocomial infections represent the most serious danger: they are in fact, responsible for the onset of sepsis, often severe, that reopens the ductus, and the long term ventilation resulting in permanent lung damage. We therefore have to do our best to improve survival of VLBW infants reducing the clinical complications that could affect these infants during their first weeks of life.

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