The Turkish Journal of Pediatrics 1998; 40: 35-44

CHRONIC LUNG DISEASE OF THE VERY LOW BIRTH WEIGHT INFANT – IS IT PREVENTABLE?*

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SUMMARY: Ogawa Y. (Professor of Pediatrics, Saitama Medical Center, Saitama Medical School, Saitama, Japan). Chronic lung disease in the very low birth weight infant - is it preventable? Turk J Pediatr 1998; 40: 35-44.

In Japan, chronic lung disease (CLD) is defined as an oxygen requirement greater than that obtainable in room air at 28 days of age, with symptoms of persistent respiratory distress and a hazy or emphysematous and fibrous appearance upon chest x-ray. A total of 4964 infants weighing less than 1500 g at birth and born in 1990 were admitted to and cared for at level II and III neonatal care centers in Japan. A total of 4293 infants (86.3%) survived at 28 days after birth.

Analyses of infants who developed CLD through their preceding illnesses and chest x-ray findings resulted in the classification of CLD into six types. Types I and II are defined as CLD following the acute stage respiratory distress syndrome (RDS). Type I is the typical case of bronchopulmonary dysplasia (BPD) as described previously, whereas Type II shows atypical radiological findings, namely only diffuse haziness without typical emphysema and fibrosis. Type III has a history of intrauterine inflammation. Chest x-ray shows the typical bubbling and cystic appearance described in the original report of Wilson-Mikity syndrome or neonatal pulmonary emphysema in the very low birth weight infant. Type III also has atypical radiological findings in cases with intrauterine infection. Type IV does not have a history of either intrauterine inflammation or RDS but shows typical emphysematous and fibrous appearance upon chest x-ray. Type V includes those with atypical chest x-ray appearance similar to Type II but without history of RDS and intrauterine inflammation.

CLD is a heterogeneous condition which shows different spectra. However, the cardinal event is common to all types - the excessive inflammatory response caused by various insults to the immature airways and alveoli, such as oxygen, barotrauma, infection and so on. The excessive inflammatory response leads to lung tissue damage and the abnormal healing process due to immaturity, (such as vitamin A deficiency and insufficient oxygen radical scavenging system) and results in dysplasia and metaplasia of the respiratory system. The treatment of respiratory distress due to CLD also acts as an insult to the lungs and thus forms a vicious cycle. The different spectra of the disease are most possibly attributed to the difference in the timing and the kind of insults to the lungs. In Type I and II CLD, the insults are given in the first hours of life when the infants with surfactant deficiency receive high concentrations of oxygen for stabilization before the surfactant replacement. In Type III and III' CLD the insults are most likely given before birth.

Excessive and sustained inflammatory response in the lungs with different onset times may result in the development of Types IV and V CLD. The strategy for the prevention of CLD should be different according to the origins and causes. The prevention of Types I and II CLD, or CLD following RDS, should be accomplished by successful prophylactic surfactant replacement therapy. Another procedure may be the application

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of high frequency oscillatory ventilation (HFOV) in the acute stage of RDS or at the time of stabilization right after birth. Types III and III' CLD present the most difficult challenge for prevention strategy because the disease process already started before birth. At the moment there are no effective measures for prevention. The strategy for the prevention of Types IV and V CLD may reside in the early detection and treatment of patent ductus arteriosus, sepsis and airway infection including pneumonia. *Key words: chronic lung disease, very low birth weight infant, classification, pathogenesis, prevention.*

Neonatal Mortality in Japan

The Committee on the Newborn of the Japan Pediatric Society has been conducting every five years the nationwide survey on the mortality of the very low birth weight infants who are cared for at the neonatal centers in Japan. According to the recent report[1], 50 infants born in 1990 and 132 infants in 1995 were below 500 g at birth and their neonatal mortality rates were 82.0 and 70.5 percent, respectively. The mortality of infants weighing from 500 to 999 g at birth improved from 26.9 percent in 1990 to 21.8 percent in 1995. When the infants weigh more than 700 g, there is more than an 85 percent chance of survival in our country at present (Fig. 1).

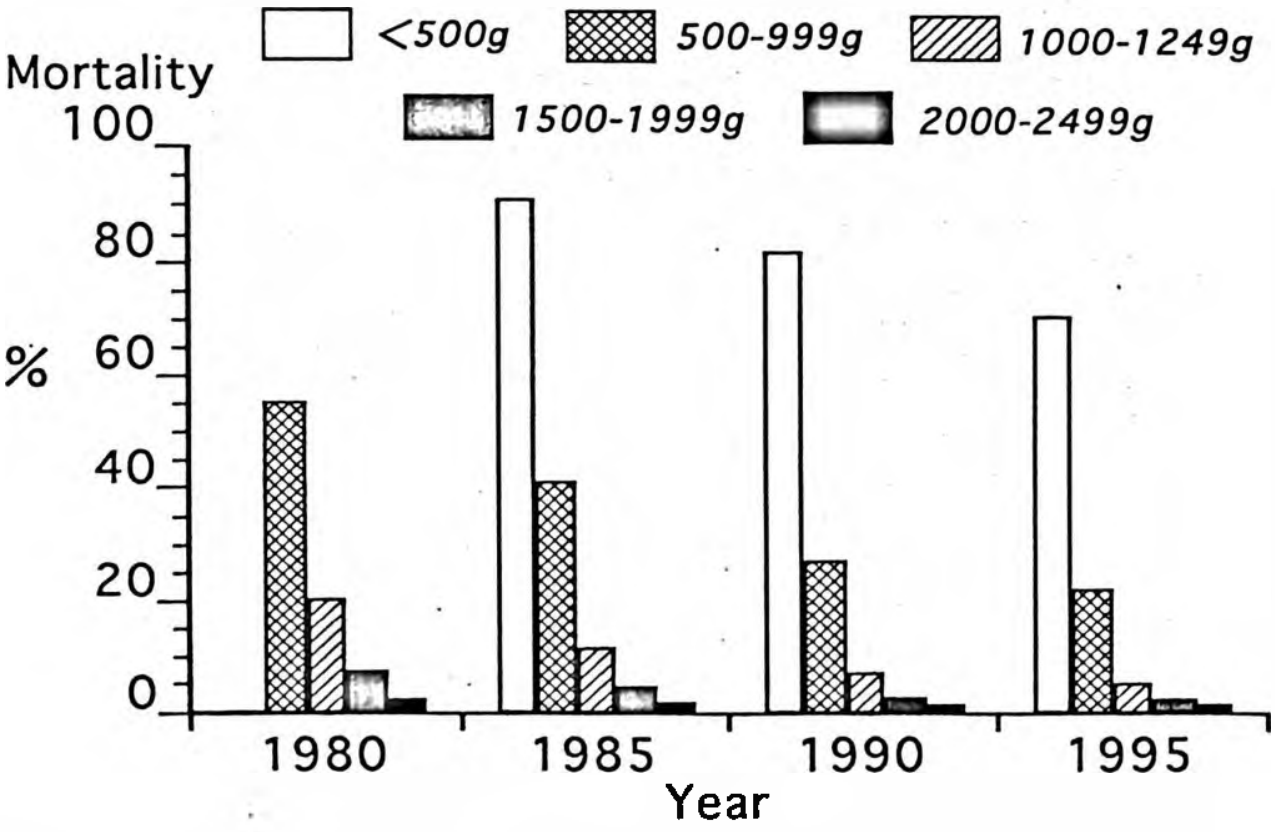

Fig. 1: Neonatal mortality rates by birth weight groups in Japan. No data for < 500 g infants born in 1980 were available. Statistically significant reduction in mortality was observed again in 1995 with the weight groups of 500 to 999 g and 1,000 to 1,499 g when compared with the data for 1990 (The Committee on the Newborn, Japan Pediatric Society, 1996).

However, follow-up study at the age of three years on the surviving extremely low birth weight infants (below 1,000 g) revealed that approximately 25 percent of them are suffering from a variety of sequelae, and pulmonary sequelae mostly due to chronic lung disease (CLD) accounted for approximately 5 percent[2]. Thus, the establishment of a strategy for the effective treatment and prevention of CLD should be most urgent and important at the present time.

Incidence of CLD

According to a previous report[3], nearly 50 percent of neonatal survivors weighing less than 1,000 g at birth are thought to be affected with CLD. In past reports, CLD was simply defined as a condition that requires an extra oxygen inhalation beyond 28 days after birth. However, this definition may result in the overdiagnosis of CLD. Many premature infants with apnea are given low concentrations of oxygen beyond 28 days after birth without any signs of chronic respiratory distress.

A nationwide survey for the incidence of CLD in infants born in 1990 was conducted with a newly established definition[4]. CLD was defined as an oxygen requirement greater than that obtainable in room air at 28 days of age, with symptoms of persistent respiratory distress and a hazy or emphysematous and fibrous appearance upon chest x-ray. Respiratory distress caused by congenital anomalies of the respiratory system was excluded.

A total of 4,964 infants weighing less than 1,500 g at birth and born in 1990 were admitted to and cared for at 301 level II and III neonatal care centers in Japan. Those infants comprised approximately 90 percent of total very low birth weight infants born in Japan. There were 1,817 infants with a birth weight below 1,000 g. A total of 4,293 infants (86.3%) survived at 28 days after birth and neonatal mortality rates decreased consistently with each 100 g weight group (Fig. 2). The survival rates in infants weighing below 1,000 g and between 1,000 and 1,499 g at birth were 73.7 and 93.9 percent, respectively.

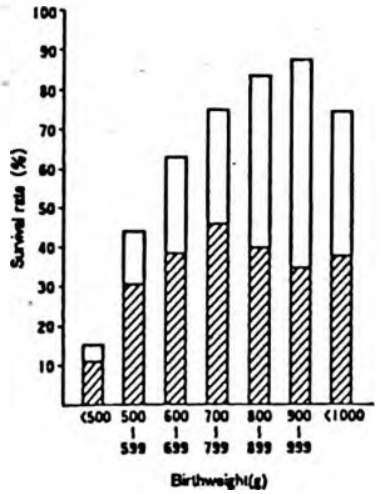

Fig. 2: The survival rates (total column length) and the rates of survivals without CLD (shaded column) by birth weight groups in the extremely low birth weight infants born in 1990 in Japan.

A total of 981 (22.9%) neonatal survivors were registered as having CLD. The decreasing incidence was consistently observed with increased birth weight. There was a 48.2 percent incidence of CLD among neonatal survivors with a birth weight below 1,000 g and an 11.3 percent incidence among infants weighing between 1,000 g and 1,499 g (Fig. 2, Table I).

Table I: Survival and Incidence of CLD by Birth Weight

		Survival at 28 Days		CLD	
Birth Weight (g)	No. of Infants Admitted	No.	%	No.	%
< 500	60	9	15.0	7	77.8
500 - 599	150	66	44.0	44	66.7
600 - 699	316	199	63.0	113	56.8
700 - 799	389	291	74.8	168	57.7
800 - 899	394	329	83.5	153	46.5
900 - 999	508	445	87.6	161	36.2
1000 - 1249	1376	1284	93.3	239	18.6
1250 - 1499	1771	1670	94.3	96	5.7
Total	4964	4293	86.5	981	22.9

Classification of CLD

Analyses of 981 infants who developed CLD through their preceding illnesses and chest x-ray findings resulted in the classification of CLD into six types (Fig. 3). Types I and II are defined as CLD following the acute stage of respiratory distress syndrome (RDS). Type I is the typical case of bronchopulmonary dysplasia (BPD) as initially reported by Northway et al.[5]. The difference in Types I and II resides in the chest x-ray findings. Type I shows the typical findings compatible to the original description by Northway et al.[5]. On the other hand, Type II shows atypical findings, namely only diffuse haziness without typical emphysema and fibrosis.

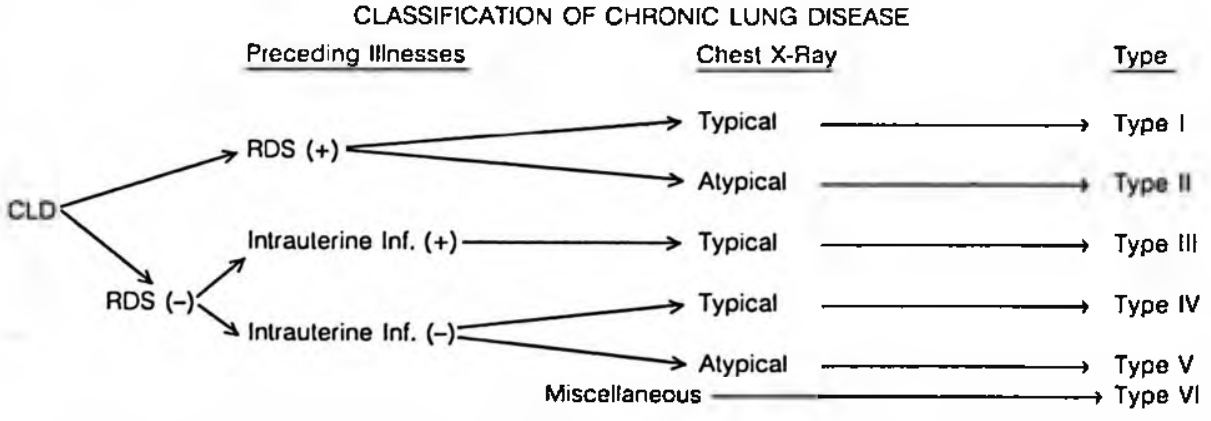

Fig. 3: Classification of chronic lung disease by preceding illnesses and chest x-ray findings (Ogawa Y, et al., 1992).

Type III has a history of intrauterine inflammation evidenced by high IgM levels at or shortly after birth, or histological proof of chorioamnionitis of the placenta or funisitis. Chest x-ray shows the typical bubbling and cystic appearance described in the original report of Wilson-Mikity syndrome[6] or in neonatal pulmonary emphysema of the very low birth weight infant reported by Fujimura et al.[7].

Type IV does not have the history of either intrauterine inflammation or RDS but shows typical emphysematous and fibrous appearance upon chest x-ray.

Type V includes those with atypical chest x-ray appearance similar to Type II but without a history of RDS and intrauterine inflammation.

Approximately 61 percent of infants developed CLD namely Types I and II following the acute stage of RDS in spite of surfactant replacement therapy with surfactant-TA shortly after birth. However, nearly half of them showed a hazy appearance and not a typical emphysematous and fibrous shadow on chest x-ray and were classified into Type II (Table II).

Table II: Distribution of CLD and Mortality by Type

Type	No. of Infants	%	Mortality	%
I	288	29.4	27	9.4
II	312	31.8	14	4.5
III	142	14.5	15	10.6
IV	118	12.0	3	2.5
V	121	12.3	6	5.0
Total	981	100.0	65	6.6

A total of 142 very low birth weight infants (14.5%) developed the type of CLD reported as neonatal pulmonary emphysema of Wilson-Mikity syndrome, or Type III. All of them had a history of intrauterine inflammation evidenced by the elevated serum IgM at birth or by histologically proven chorioamnionitis of the placenta.

The remaining 239 infants did not have RDS nor the apparent evidence of intrauterine inflammation. Approximately half of them, 118 infants, showed a typical x-ray appearance and were classified as Type IV. However, chest x-ray findings were hazy in 121 infants, and they were classified into Type V.

The overall mortality was 6.6 percent. Infants classified into Type III showed the worst rate (10.6%) and Type I had 9.4 percent (Table II). The poor prognosis of Type III prompted us to survey further. In 1992, a total of 178 infants from eight major neonatal centers weighing below 1,500 g at birth who had serum IgM levels over 30 mg/dl within 24 hours after birth were studied. One hundred and fifty infants or 84.3 percent survived their first month. Among these neonatal

survivors, 35 infants had RD and 28 of them (80%) developed CLD. The CLD infants were equally divided in Type I and II. On the other hand, among 115 infants without RDS, 52 infants (or 45.2%) developed CLD. Thirty-seven infants (or 71.2%) showed a typical bubbly appearance on chest x-ray and were classified as Type III. However, 15 out of 52 infants (or 28.8%) showed only diffuse haziness similar to Type II (Fig. 4). Therefore, a new group, Type III; was added to the classification and this revised classification has been adopted for the recent nationwide survey conducted on the infants born in the year of 1995 (Fig. 5).

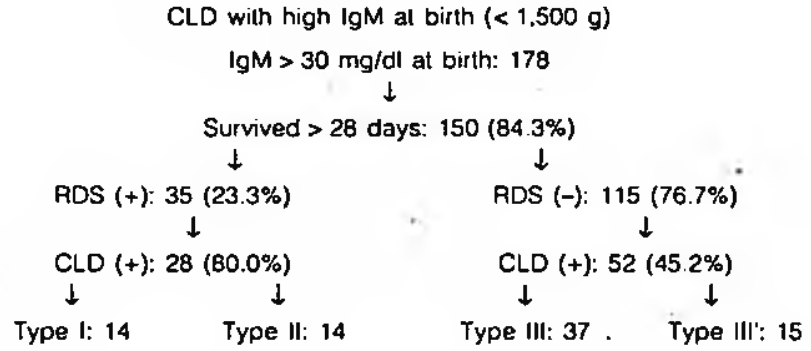

Fig. 4: Surveys on the very low birth weight infants with high serum IgM levels at birth and chronic lung disease.

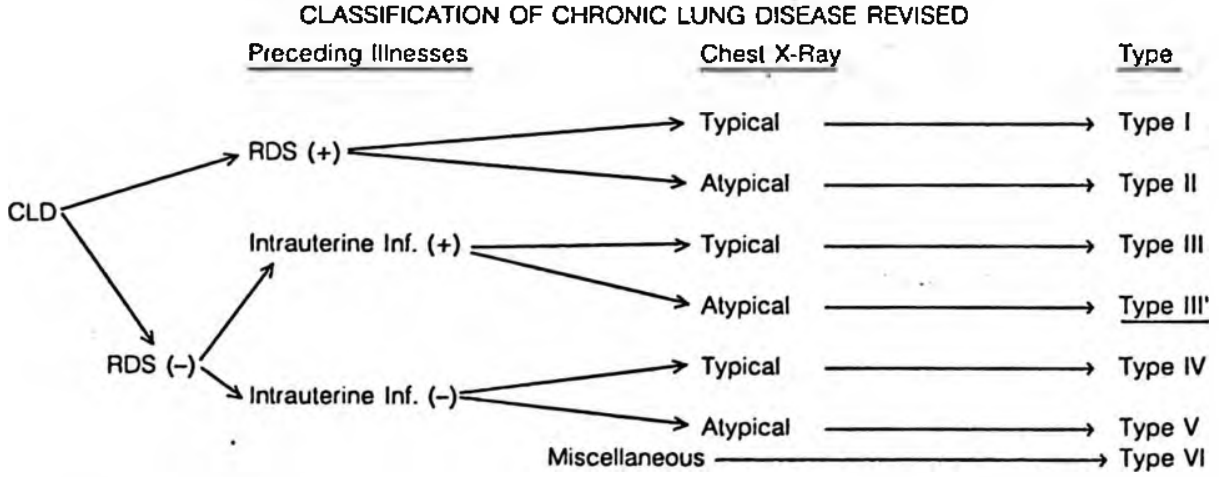

Fig. 5: Revised classification of chronic lung disease. Type III CLD following intrauterine inflammation but with atypical x-ray appearance was added to the previous classifications.

Pathophysiology of CLD

CLD is a heterogeneous condition which shows different spectra. However, the cardinal event is common to all types-the excessive inflammatory response caused by various insults to the immature airways and alveoli, such as oxygen, barotrauma, infection and so on. The excessive inflammatory response leads to the lung tissue damage and the abnormal healing process due to immaturity,

such as vitamin A deficiency and an insufficient oxygen radical scavenging system, and results in dysplasia and metaplasia of the respiratory system. The treatment of respiratory distress due to CLD also acts as an insult to the lungs and creates a vicious cycle. The different spectra of the disease are most possibly attributed to the difference in the timing and the kinds of insults to the lungs.

Our studies have shown the important roles of several cytokines and chemical mediators in the development of CLD[8-10]. Recent studies demonstrated the increased concentration of granulocyte elastase α 1-proteinase inhibitor complex in the tracheobronchial aspirates of Type III infants in the first 48 hours of life[7, 11]. Interleukin-8 (IL-8), which is known as a potent chemoattractant of the granulocyte, is also significantly higher in the tracheal aspirates within 48 hours of life from infants with Type III CLD[11]. These data suggest that the insult causing the lung damage occurred shortly before birth.

On the other hand, in infants with Types I and II CLD or CLD following RDS, granulocyte elastase α 1-proteinase inhibitor complex levels in the tracheobronchial aspirates remain low in the first hours of life but start to rise after 48 hours[12]. Similarly, the levels of IL-8 in the tracheobronchial aspirates of infants with Types I and II CLD remain low in the first 48 hours but start to rise thereafter[12]. Interestingly, there is a good correlation between FiO2 within 48 hours of life and IL-8 concentrations in the tracheobronchial aspirates taken between 48 hours after birth and day five, which suggests that one of the most potent insults to the lungs for CLD might be the high concentration of oxygen given for stabilization in the first hours of life[12].

Granulocyte elastase α 1-proteinase complex levels in the tracheobronchial aspirates from infants with Types IV and V CLD show various rising patterns after 48 hours of life[13]. IL-8 also shows a similar pattern as seen in granulocyte elastase α 1-proteinase complex[13]. The area under the curve from day 0 to 28 depicting the concentrations of these two agents is significantly higher in infants with Types IV and V CLD than in infants who did not develop CLD.

The achievements in our laboratory and from others may lead us to conclude that different causative insults to the lungs with different timings will produce different spectra of the disease, though the inflammatory response of the lungs is a common pathophysiology. In Types I and II CLD, the insults are given in the first hours of life when the infants with surfactant deficiency receive high concentrations of oxygen for stabilization before the surfactant replacement. In Types III and III' CLD our data clearly support the idea that the insults are most possibly given before birth. At the moment it is not possible to identify the specific insult(s) clearly, but certain kinds of infection are highly suspected.

In our survey, approximately 53 percent of infants with high IgM levels at birth developed CLD. Excessive inflammatory response in the lungs in the perinatal period may be the cardinal event in this type of CLD. On the other hand,

excessive and sustained inflammatory response in the lungs with different onset times may result in the development of Types IV and V CLD. Our previous studies revealed that, in addition to IL-8 and granulocyte elastase, other cytokines and chemical mediators such as platelet-activating factor (PAF)[10], leukotrienes[14], and tumor necrosis factor (TNF)-α[15] are present in increased amounts in the tracheobronchial aspirates from infants with symptomatic patent ductus arteriosus, sepsis and pneumonia.

Strategy for Prevention of CLD

The strategy for the prevention of CLD should be different according to the origins and causes because, as mentioned above, the different times of onset and causes result in the different spectra of the disease.

The prevention of Types I and II CLD, or CLD following RDS, should be achievable with successful prophylactic surfactant replacement therapy. Meta-analysis of prophylactic administration studies showed the event rate ratio as 0.75, namely, approximately 25 percent reduction of CLD by the treatment. A recent trial in Japan also showed significant reduction of severe CLD by the prophylactic administration of surfactant-TA as soon as the surfactant deficiency was proven by a stable microbubble rating on the gastric aspirates at birth[16]. In our nationwide survey almost half of the infants with a history of RDS who later developed CLD showed atypical x-ray findings and were classified as Type II;[3] classifications into this group further increased in infants born in 1995. It could be speculated that most of the infants classified into Type II might have developed Type I CLD or typical BPD, if they had not been given exogenous surfactant in the acute stage of RDS. Thus, the strategy for the prevention of CLD following RDS (Types I and II) resides in the application of a simple and quick method for detecting surfactant deficiency at birth and administration of prophylactic surfactant replacement therapy.

Another procedure may be the application of high frequency oscillatory ventilation (HFOV) in the acute stage of RDS or at the time of stabilization right after birth. HFOV can reduce the inspired oxygen concentration quickly and prevent barotrauma caused by the conventional ventilation in which a large volume and high pressure are applied.In addition, our recent study has demonstrated the reduction of the surfactant consumption by HFOV.

Types III and III' CLD are the most difficult to prevent, because the disease process starts before birth. At the moment there are no effective measures for prevention. Further research into the pathogenic process of these types of CLD by an interdisciplinary team of obstetricians and neonatologists is necessary.

Strategy for the prevention of Types IV and V CLD may reside in the early detection and treatment of patent ductus arteriosus, sepsis and airway infection, including pneumonia. The excessive hydration often causes symptomatic patent ductus arteriosus. Therefore, all very low birth weight infants should be nursed and cared for in the closed incubator with the minimum necessary amount of hydration. Care in the radiant warmer bed with a large amount of hydration should be avoided.

The early detection of infection may be accomplished by the application of acute phase reactants score (APR score). It is a scoring system for the elevation of three acute phase proteins, CRP, α-1-acid glycoprotein and haptoglobin, in case of acute infection[17]. The elevation of all three proteins above normal limits is scored as three and interpreted as the presence of acute bacterial infection. The levels of those three proteins can be measured in a few minutes with a minimum amount of blood samples.

Screening for infection and early treatment in the very low birth weight infant should contribute to the reduction of Types IV and V CLD.

A recent study reported that the congenital alveolar proteinosis has a surfactant protein B (SP-B) deficiency due to a genetic anomaly and that patients with some types of SP-B deficiency may possibly be diagnosed as having CLD of unknown causes, or Type VI CLD[18]. The ultimate strategy for this type of CLD may be gene transfer therapy.

Our final goal is the prevention of the preterm births. Meanwhile, the correct diagnosis and classification of CLD should be adopted in all studies and surveys in order to establish the strategy for the prevention and effective treatment of all types of CLD.

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