

Original Article

Efficiency of high-frequency oscillatory ventilation combined with pulmonary surfactant in the treatment of neonatal meconium aspiration syndrome

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Abstract: The aim of this study was to investigate the clinical efficiency of the use high-frequency oscillatory ventilation (HFOV) combined with pulmonary surfactant (PS) for the treatment of neonatal meconium aspiration syndrome (MAS). Clinical data of 53 MAS patients admitted to neonatal intensive care unit (NICU) was collected and the patients were divided into 3 groups according to the different treatment approach: group 1 conventional mechanical ventilation (CMV); group 2 HFOV; group 3 HFOV + PS. By monitoring the changes in oxygenation function indicators such as inhaled oxygen concentration (FiO_2), oxygenation index (OI) and arterial oxygen tension/alveolar arterial oxygen tension (a/ApO_2) of three groups after 2, 12, 24, 48 h of treatment, the usage of the ventilator, duration of hospitalization, changes in clinical manifestations and outcomes of three groups were analyzed. As compared to group 1, the difference in all the oxygenation function indicators after treatment in group 2 and group 3 was statistically significant at different points in time ($P < 0.05$). However, the timing and extent of the change in the indicators in group 3 were more significant than in group 2; as compared to group 1, the ventilation time, duration of the oxygen therapy and hospitalization time of group 2 and group 3 were significantly shorter and the difference was statistically significant ($P < 0.05$). Early use of HFOV combined with PS to treat MAS has significant therapeutic effect, especially for the treatment of severe MAS where it can be used as a safer and more effective rescue measure.

Keywords: High-frequency oscillatory ventilation, pulmonary surfactant, meconium aspiration, neonates

Introduction

Meconium aspiration syndrome (MAS) is one of the most common causes of severe respiratory failure in infants born at term or postterm gestation, and also one of the serious diseases during the neonatal period where the fetus inhales meconium-stained amniotic fluid (MSAF), prior to delivery or during the delivery, causing mechanical obstruction and chemical inflammation along the respiratory tract and the alveolar, hereby simultaneously causing other organ damages. Meconium staining of the amniotic fluid occurs in approximately 10% to 20% of all term deliveries, but MAS occurs in fewer than one-third of these infants [1]. But RY and Rao A have reported, about 10% MAS resulted in respiratory failure in developing countries, the mortality rate was up to 39% [2].

The clinical treatment often opted for MAS is mechanical ventilation; conventional mechanical ventilation (CMV) can easily cause barotrauma and/or volutrauma, high-frequency oscillatory ventilation (HFOV) is a new method of ventilation which is characterized by an effective gas exchange using tidal volumes equal to or less than the dead space volume at supraphysiological frequencies, and by means of high-frequency oscillations, produces biphasic pressure changes, hence achieving efficient ventilation/oxygenation function [3, 4]. Surfactant replacement therapy has been proven beneficial in the prevention and treatment of neonatal respiratory distress syndrome (NRDS). The deficiency of surfactant or surfactant dysfunction may contribute to respiratory failure in a broader group of disorders, including MAS. In infants with MAS, pulmonary surfactant administration

may reduce the severity of respiratory illness and decrease the number of infants with progressive respiratory failure requiring support with extracorporeal membrane oxygenation (ECMO) [5]. Curosurf, also known as pig lung surfactant, can improve the clinical manifestations of respiratory distress caused by meconium aspiration [6]. This retrospective analysis of the 53 cases of MAS registered in our hospital, is to investigate the clinical efficiency of the use of high frequency oscillation ventilation combined with pulmonary surfactant (Curosurf) in the treatment of MAS.

Methods

Subjects

The medical records of patients were retrieved and a retrospective analysis was conducted. Clinical data of 53 MAS patients admitted to NICU of our faculty during the period June 2010 to June 2013 was collected; among which there were 31 males and 22 females, hence the male to female ratio was 1.4:1. Among the patients, there were 19 cases of natural delivery and 34 cases of cesarean section; there were 11 cases with 1 minute after birth Apgar score 1-3 points, 26 cases with 4-7 points and 16 cases with 8-10 points; out of the 53 cases, there were 44 full-term delivery while there were 9 cases of preterm delivery (3 cases in group 1, 5 cases in group 2 and 1 case in group 3, there were 2 cases where the gestational age < 35 weeks). There were 2 cases where the birth weight (BW) < 1500 g and 6 cases where BW < 2500 g. After birth, the blood gas analysis normally presented a low pH and indicated the presence of respiratory acidosis. There were 6 cases of pneumothorax and 13 cases of pulmonary hypertension in group 1; in group 2, there were 4 cases of pneumothorax and 11 cases of pulmonary hypertension while in group 3, there were 2 cases of pneumothorax and 7 cases of pulmonary hypertension. The pneumothorax and pulmonary hypertension situation of the three groups is quite comparable. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Quanzhou Maternal and Children's Health Hospital. Written informed consent was obtained from all participants.

Grouping

According to the different approach of treatment, the patients were divided into 3 groups: group 1 comprised of 23 cases using conventional mechanical ventilation (CMV); group 2 comprised of 18 cases using high-frequency oscillatory ventilator (HFOV) while group 3 comprised of 12 cases using high-frequency oscillatory ventilation combined with PS (Curosurf).

Use of protective mechanical ventilation

Drager Baby Log 8000 ventilator (Germany) or PB840 ventilator (the United States) was used for CMV while SLE5000 ventilators (UK) were used for HFOV. CMV was basically set on pressure control and on synchronized intermittent mandatory ventilation (SIMV) mode where the default parameters for CMV were: fraction of inspiration O_2 (FiO_2) 50-80%, respiratory rate (RR) 30-50 beat per minute (bpm), peak inspiratory pressure (PIP) 18-25 cm H_2O , positive end-expiratory pressure (PEEP) 4-6 cm H_2O , inspiratory time (Ti) 0.4-0.5 s. The default parameters set for HFOV were FiO_2 50-80%; the frequency at 9-11 Hz; mean airway pressure (MAP) 10-17 cm H_2O while for patients with pneumothorax, MAP was toned down to 10-13 cm H_2O . The oscillation amplitude of 40-60 cm H_2O was gradually adjusted to the point where the amplitude of respiratory movement of the chest of the patient was obvious. The parameters of the ventilator were adjusted accordingly to the results of the blood gas analysis and transcutaneous oxygen saturation (SaO_2). In cases of hypoxemia, FiO_2 was increased by 5-10% with or without an increase of 1-2 cm H_2O in the PIP or an increase of 2-3 cm H_2O in the amplitude. In cases of hypercapnia, the parameters of CMV were adjusted with an increase of 5-10 bpm in the RR with or without an increase of 1-2 cm H_2O in the PIP. However, on the other hand, in case of hypercapnia, the parameters for HFOV were adjusted with a decrease of 1-2 Hz in the oscillation frequency, an increase of 5-10% in the amplitude and an increase of 1-2 cm H_2O in MAP.

Use of pulmonary surfactant

PS (Curosurf) was manufactured by Chiesi Farmaceutici S.p.A. (Italy), 120 mg/injection or 240 mg/injection. It is recommended that treatment should be started as early as possi-

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Table 1. Comparison of the clinical data of the 3 groups of patients

Group	Cases (n)	Age upon admission (d)	Fetal Age (weeks)	Birth Weight (kg)
1	23	0.79±0.76	39.15±1.32	2.68±0.87
2	18	0.81±0.69	38.87±0.93	2.77±0.59
3	12	0.83±0.71	39.24±1.14	2.80±0.72
F-value		3.074	1.856	2.367
P-value		P > 0.05	P > 0.05	P > 0.05

Note: P > 0.05 indicates that the difference in the clinical data among the three groups is not statistically significant.

ble after diagnosis in order to ensure early intervention. Method of usage [7]: After clearing the airway, PS is administered through the endotracheal tube, the dosage is (100-200) mg/kg each time. We had four cases where PS was used at a dosage of (100-150) mg/kg each time, eight cases with the dosage (150-200) mg/kg each time and after every administration, bag-mask ventilation was performed for 10-15 min to ensure that uniform distribution of PS is achieved in the lungs. There were also 3 cases where PS treatment was administered twice.

Monitoring indicators

By monitoring the changes in the oxygenation function indicators such as fraction of inspiration O₂ (FiO₂), oxygenation index (OI) and arterial oxygen tension/alveolar arterial oxygen tension (a/ApO₂) of the three groups after 2, 12, 24, 48 h of treatment, usage of the ventilator, duration of hospitalization, changes in clinical manifestations and outcomes of the three groups were retrospectively analyzed.

Diagnostic criteria

The diagnosis of MAS was defined according to the following criteria, which basically consisted of history of fetal distress or asphyxia during delivery; thick meconium-stained amniotic fluid; meconium particles visible below the glottis; breathing difficulties combined with type II respiratory failure soon after birth; thoracic X-ray with pulmonary granular and patchy shadows [8].

Statistical analysis

The results were statistically analyzed using the SPSS 16.0 statistical software. Data was represented by mean ± standard deviation ($\bar{x} \pm$

s) and was analyzed by the SPSS16.0 statistical software where the differences among the three groups were compared by analysis of variance, where P < 0.05 is considered statistically significant.

Results

Clinical data

Age upon admission, fetal age and birth weight were no significant difference in three groups (P > 0.05, **Table 1**).

Changes in the pulmonary oxygenation indicators

Compared to group 1, the difference in all the oxygenation function indicators after treatment in group 2 and group 3 at different points in time, was statistically significant (P < 0.05). However, the timing and extent of the change in the indicators in group 3 were more obvious than group 2 (**Tables 2, 3**).

Various parameters of the ventilator

Before mechanical ventilation, the three indicators FiO₂, OI and a/ApO₂ showed no significant difference in all of three groups of patients (P > 0.05). Compared to group 1 and group 2, after the usage of PS, there was notable decrease in the ventilator indicators FiO₂ and MAP in group 3 patients at different points in time, and the difference was found to be statistically significant (P < 0.05, **Table 4**).

Duration of hospitalization, complications and outcome

As compared to group 1, the ventilation time, duration of the oxygen therapy and hospitalization time of group 2 and group 3 were significantly shorter, the difference was found to be statistically significant (P < 0.05). However, there was no significant statistical difference in the mortality rate of the patients and in the incidence of group 3 or higher degree of cranial hemorrhage in three groups (P > 0.05, **Table 5**).

Discussion

MAS is complex respiratory disease of the term and near-term neonate, which continues to place a considerable burden on neonatal intensive care resources worldwide [9, 10]. Fetal dis-

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Table 2. Comparison of the OI of the 3 groups before and after ventilation at different points in time

Group	Cases (n)	Before ventilation	2 h	12 h	24 h	48 h
1	23	25.48±8.27	23.79±7.27	17.64±4.83	15.48±3.97	15.04±4.76
2	18	25.03±7.81	21.13±6.29 ^a	13.51±4.45 ^a	12.36±4.16 ^a	11.73±4.54 ^a
3	12	26.12±6.57	18.35±5.68 ^{a,b}	10.25±3.57 ^{a,b}	9.24±4.52 ^{a,b}	7.85±5.06 ^{a,b}
F-value		2.254	6.125	7.651	9.384	11.238
P-value		<i>P</i> > 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.01

Note: As compared with group 1, group 2 and group 3 ^a*P* < 0.05, as compared with group 2, group 3 ^b*P* < 0.05.

Table 3. Comparison of the a/ApO₂ of the 3 groups before and after ventilation at different points in time

Group	Cases (n)	Before ventilation	2 h	12 h	24 h	48 h
1	23	0.09±0.07	0.11±0.04	0.15±0.03	0.24±0.13	0.31±0.07
2	18	0.09±0.08	0.14±0.06 ^a	0.18±0.05 ^a	0.30±0.09 ^a	0.35±0.06 ^a
3	12	0.09±0.06	0.17±0.03 ^{a,b}	0.23±0.07 ^{a,b}	0.35±0.05 ^{a,b}	0.40±0.02 ^{a,b}
F-value		1.953	6.706	7.028	7.658	8.124
P-value		<i>P</i> > 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05

Note: As compared with group 1, group 2 and group 3 ^a*P* < 0.05, as compared with group 2, group 3 ^b*P* < 0.05.

Table 4. Comparison of the FiO₂ of the 3 groups before and after ventilation at different points in time

Group	Cases (n)	Before ventilation	2 h	12 h	24 h	48 h
1	23	0.86±0.21	0.74±0.16	0.69±0.08	0.52±0.12	0.47±0.21
2	18	0.89±0.12	0.68±0.14 ^a	0.59±0.10 ^a	0.47±0.15 ^a	0.41±0.11 ^a
3	12	0.87±0.15	0.59±0.13 ^{a,b}	0.48±0.07 ^{a,b}	0.35±0.17 ^{a,b}	0.29±0.16 ^{a,b}
F-value		1.984	9.726	14.537	11.512	18.358
P-value		<i>P</i> > 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05

Note: As compared with group 1, group 2 and group 3 ^a*P* < 0.05, as compared with group 2, group 3 ^b*P* < 0.05.

tress during labor causes intestinal contractions as well as relaxation of the anal sphincter, which allows meconium to pass into the amniotic fluid and contaminate the amniotic fluid. Due to hypoxia, the fetus is going to experience transient apnea and then starts breathing heavily, migration of meconium down the tracheobronchial tree initially causes obstruction of airways of progressively smaller diameter, which results in respiratory infections, lung inflammation and a series of clinical manifestations [11]. MAS is most commonly seen in full-term and post term newborns than in preterm newborns. The incidence of MSAF in live births is of 9-16%, but however, only 1.2-1.6% of the cases result in MAS. The mortality rate after occurrence of MAS is of 7-15.8% [12].

Clinically, MAS is usually defined as respiratory dysfunction in an infant who is born with MSAF. MAS is a non-uniform lung disease, with characteristics such as incomplete or complete air-

way obstruction, pulmonary inflammation and inhibition of pulmonary surfactant. Many studies have shown that hypoxemia resulting in pulmonary vascular damage plays a key role in the pathogenesis of MAS [13]. These infants with MAS inhaled meconium-stained amniotic fluid, causing mechanical obstruction and inflammation along the respiratory tract and alveoli while hypoxia and acidosis cause damage to the endothelial cells and alveolar type II cells, leading to decrease pulmonary surfactant synthesis which in turn, causes a decrease in lung surface tension, hence resulting in decreased lung compliance and atelectasis [14]. Simultaneously, there is strong inflammatory response in the alveoli, causing considerable protein exudation while the chemical inflammation and inflammatory metabolites inhibit PS activity, thereby causing alveolar collapse, leading to the formation of the hyaline membrane. In vitro research states that meconium particles can cause inactivation of pulmonary surfactant,

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Table 5. Comparison of the ventilation time, duration of hospitalization, duration of the oxygen therapy and cases of intracranial hemorrhage

Group	Cases (n)	Ventilation time (d)	Hospitalization time (d)	Duration of Oxygen therapy (d)	Death Cases (%)	IVH (n)
1	23	7.24±0.65	22.17±4.53	15.39±2.44	1 (4.35)	6
2	18	4.23±1.37 ^a	15.61±3.45 ^a	11.76±5.32 ^a	1 (5.56)	4
3	12	2.91±0.5 ^{a,b}	11.75±4.3 ^{a,b}	7.36±2.15 ^{a,b}	0 (0.00)	3
F(χ^2)-value		16.237	19.661	23.549	1.0812	0.8528
P-value		<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> < 0.05	<i>P</i> > 0.05	<i>P</i> > 0.05

Note: As compared with group 1, group 2 and group 3 ^a*P* < 0.05, as compared with group 2, group 3 ^b*P* < 0.05.

hereby reducing the production of surfactant protein-A (SP-A) and surfactant protein B (SP-B) [15].

Meconium aspiration syndrome is one of the main causes of neonatal respiratory failure. Meconium obstruction in the newborn can lead to hypoxia, further causing pulmonary collapse which eventually gives rise to the right to left shunt, which furthermore intensifies hypoxemia. Therefore, about one-third of newborns with MAS require mechanical ventilation treatment. HFOV is considered a protective strategy for human lungs, and makes use of a smaller or approximately the same tidal volume as the anatomical dead space and ventilates at a higher frequency (more or approximately 4 times the normal frequency), achieving a special new type of ventilation with more effective gas exchange [16]. The analysis of the results reveals that when compared with group 1, the difference in the various oxygenation indicators at different points in time after treatment of group 2 and group 3 was statistically significant (*P* < 0.05); the ventilation time, duration of oxygen therapy and hospitalization time of group 2 and group 3 were significantly shorter, and the difference was statistically significant (*P* < 0.05); indicating that HFOV has significant therapeutic effect in treating MAS. As compared to the normal frequency ventilation, HFOV has advantages such as low tidal volume, low airway pressure, low-cut cavity pressure and positive end-expiratory pressure, which avoid making the alveoli open and close repeatedly, causing no shear force, keeping the alveoli under continuous uniform expansion, hence maintaining effective aeration and ventilation. The low airway pressure can reduce barotrauma, and also does not conflict with the newborn's individual spontaneous breathing [17, 18].

Poractant alfa injection, also known as Curosurf, is an extract of natural porcine lung surfactant, containing 41-48% of lecithin, 51-58% of other phospholipids hydrophobin and 1% hydrophobic low molecular weight proteins. These infants with MAS complement Curosurf exogenously where PS covers the alveolar surface, reducing alveolar surface tension and preventing end-expiratory alveolar collapse in order to maintain functional residual capacity, stable alveolar pressure and hence reduce the exudation of fluid from the capillaries to the alveoli. The analysis of the results of this research reveals that when compared to group 1 and group 2, after treatment, the change in the various oxygenation indicators of group 3 were more significant in function of the timing and extent. After the PS treatment, the ventilator parameters FiO₂, OI, and MAP of the newborns of group 3 decreased significantly at different points in time, and the difference was found to be statistically significant. The results suggest that the combination of complementing PS exogenously and the use of HFOV play a very important role in the treatment of MAS where they can rapidly improve the clinical manifestations, hence decreasing the time of mechanical ventilation and exposure to high concentration of oxygen [19, 20]. Collaborative Chinese Multicenter Study Group for neonatal respiratory diseases confirmed that the use of exogenous PS in the treatment of severe neonatal respiratory failure caused by MAS, can improve the efficiency of pulmonary oxygenation and ventilation [21]. Herting and other studies have found that PS improves oxygenation functions in majority of neonatal pneumonia [22]. However, the analysis of the results of this study found out that the difference of mortality rate and occurrence of over third degree intracranial hemorrhage in the three groups

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was not statistically significant, hereby stating that PS treatment can significantly improve oxygenation function in the patients, but cannot significantly alter the occurrence of serious complications and the prognosis of these infants with MAS.

In summary, the early use of high-frequency oscillatory ventilation combined with pulmonary surfactant to treat MAS has significant effect, especially for the treatment of severe MAS, where it can be used as a safer and more effective rescue measure.

Disclosure of conflict of interest

None.

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References

- [1] Hutton EK and Thorpe J. Consequences of meconium stained amniotic fluid: what does the evidence tell us? *Early Hum Dev* 2014; 90: 333-339.
- [2] Bhat RY and Rao A. Meconium-stained amniotic fluid and meconium aspiration syndrome: a prospective study. *Ann Trop Paediatr* 2008; 28: 199-203.
- [3] Sánchez Luna M, Santos González M and Tendillo Cortijo F. High-Frequency Oscillatory Ventilation Combined with Volume Guarantee in a Neonatal Animal Model of Respiratory Distress Syndrome. *Crit Care Res Pract* 2013; 2013: 593915.
- [4] Slutsky AS, Drazen FM, Ingram RH Jr, Kamm RD, Shapiro AH, Fredberg JJ, Loring SH and Lehr J. Effective pulmonary ventilation with small-volume oscillations at high frequency. *Science* 1980; 209: 609-671.
- [5] El Shahed AI, Dargaville PA, Ohlsson A and Soll R. Surfactant for meconium aspiration syndrome in term and late preterm infants. *Cochrane Database Syst Rev* 2014; 12: CD002054.
- [6] Choi HJ, Hahn S, Lee J, Park BJ, Lee SM, Kim HS and Bae CW. Surfactant lavage therapy for meconium aspiration syndrome: a systematic review and meta-analysis. *Neonatology* 2012; 101: 183-191.
- [7] Gizzi C, Papoff P, Barbàra CS, Cangiano G, Midulla F and Moretti C. Old and new uses of surfactant. *Matern Fetal Neonatal Med* 2010; 23 Suppl 3: 41-44.
- [8] Louis D, Sundaram V, Mukhopadhyay K, Dutta S and Kumar P. Predictors of mortality in neonates with meconium aspiration syndrome. *Indian Pediatr* 2014; 51: 637-640.
- [9] Dargaville PA. Respiratory support in meconium aspiration syndrome: a practical guide. *Int J Pediatr* 2012; 2012: 965159.
- [10] Yurdakök M. Meconium aspiration syndrome: do we know? *Turk J Pediatr* 2011; 53: 121-129.
- [11] Bouziri A, Hamdi A, Khaldi A, Bel Hadj S, Menif K and Ben Jaballah N. Management of meconium aspiration syndrome with high-frequency oscillatory ventilation. *Tunis Med* 2011; 89: 632-637.
- [12] Wiswell TE. Advances in the treatment of meconium aspiration syndrome. *Acta Paediatr* 2001; 90: 28-30.
- [13] Mikolka P, Mokrá D, Kopincová J, Tomčíková-Mikušiaková L and Calkovská A. Budesonide added to modified porcine surfactant curosurf may additionally improve the lung functions in meconium aspiration syndrome. *Physiol Res* 2013; 62 Suppl 1: S191-200.
- [14] Mokra D and Calkovska A. How to overcome surfactant dysfunction in meconium aspiration syndrome? *Respir Physiol Neurobiol* 2013; 187: 58-63.
- [15] Wang H, Gao X, Liu C, Yan C, Lin X, Yang C, Lin Z, Zhu W, Yang Z, Yu F, Qiu Y, Liu X, Zhou X, Chen C and Sun B. Morbidity and mortality of neonatal respiratory failure in China: surfactant treatment in very immature infants. *Pediatrics* 2012; 129: e731-740.
- [16] Moniz M, Silvestre C, Nunes P, Abadesso C, Matias E, Loureiro H and Almeida H. High-frequency oscillatory ventilation in children: a 10-year experience. *J Pediatr* 2013; 89: 48-55.
- [17] Singh SN, Malik GK, Prashanth GP, Singh A and Kumar M. High frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation in preterm neonates with hyaline membrane disease: a randomized controlled trial. *Indian Pediatr* 2012; 49: 405-408.
- [18] Fu W, Qin X, You C, Meng Q, Zhao Y and Zhang Y. High frequency oscillatory ventilation versus conventional ventilation in a newborn piglet model with acute lung injury. *Respir Care* 2013; 58: 824-830.
- [19] Sürmeli-Onay O, Korkmaz A, Yiğit S and Yurdakök M. Surfactant therapy in late preterm infants: respiratory distress syndrome and beyond. *Turk J Pediatr* 2012; 54: 239-246.
- [20] Greer SE and McCunn M. High-frequency oscillatory ventilation. *Curr Probl Surg* 2013; 50: 471-478.

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- [21] Chinese Collaborative Study Group for Neonatal Respiratory Diseases. Treatment of severe meconium aspiration syndrome with porcine lung-derived surfatant: amulticente, randomized, controlled trial. *Acta Paediatr* 2005; 94: 896-902.
- [22] Herting E, Gefeller O, Land M, van Sonderen L, Harms K and Robertson B. Surfactant treatment of neonates with respiratory failure and group B streptococcal infection. Members of the Collaborative European Multicenter Study Group. *Pediatrics* 2000; 106: 957-964.