

RECENT ADVANCES IN THE MANAGEMENT OF HYALINE MEMBRANE DISEASE

Anil Batra, Neelam Kler, Arun Soni

Department of Neonatology, Sir Ganga Ram Hospital, Rajindra Nagar, New Delhi-110060, India

Abstract : Hyaline membrane disease (HMD), also known as respiratory distress syndrome (RDS) is the most common cause of respiratory distress in preterm neonates. The greatest risk factor is low gestational age and the disease is due to inadequate pulmonary surfactant. The structurally immature and surfactant-deficient lungs have decreased compliance and a tendency to atelectasis. An eosinophilic membrane composed of a fibrinous matrix of materials from the blood and cellular debris (the hyaline membrane) lines the visible airspaces hence the term HMD. Clinical features include tachypnea, grunting and retractions in a preterm neonate usually beginning immediately or within few hours after birth. The incidence of HMD has markedly decreased by prenatal treatment with glucocorticoids. The development of surfactant is one of the great success stories in neonatal care because the therapy specifically treats the surfactant deficiency and changes the pathophysiology and outcome of HMD. Benefits of early use of CPAP are fast emerging in the management of hyaline membrane disease. Despite substantial improvements in the management of HMD, prevention is still the ultimate goal.

INTRODUCTION

Hyaline membrane disease (HMD), also known as respiratory distress syndrome (RDS) is the commonest cause of respiratory distress in preterm neonates. It occurs after the onset of breathing in neonates with insufficiency of pulmonary surfactant. The clinical diagnosis is often made in preterm infants with respiratory difficulty that includes tachypnea, retractions, nasal flaring and need for oxygen all presenting within 4-6 hours after birth. There is a reticulogranular chest X ray appearance as a result of widespread atelectasis. Pathophysiologically, this condition is characterized by non-compliant (stiff) lungs, which become atelectatic at end-expiration. Histologically, hyaline membrane formation occurs in advance stage, lining the terminal airways.

Various advances that have resulted in decrease in incidence and reduction in morbidity and mortality in neonates with HMD include

1. Use of antenatal steroids to enhance pulmonary maturity
2. Appropriate resuscitation with immediate use of continuous positive airway pressure (CPAP) for alveolar recruitment
3. Early administration of surfactant
4. Using gentle modes of ventilation to minimize damage to the immature lungs.

These therapies have also resulted in the survival of extremely premature infants. With survival of these extremely preterm infants, there is an associated increase in the morbidities, which include patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), septicemia, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL) with associated neurodevelopmental and audiovisual handicaps. Direct attention to anticipate and minimizing these complications and to prevent premature delivery whenever possible are the strategic goals of its management.

EPIDEMIOLOGY

HMD typically affects infants <35 weeks gestational age (GA) but

may affect older infants who have delayed lung maturation. Low GA is the greatest risk factor for HMD, and its incidence varies inversely with birth weight among AGA infants (Table 1)¹. This is due to deficiency of the surfactant in these neonates which leads to decreased compliance of the lungs. The maturation of surfactant synthesis reflects the decreasing incidence of HMD with an increase in gestational age. The incidence of HMD is reported to be 6.8-14.1% of preterm live births in our country². HMD is the commonest indication of ventilation in neonates in India³. The reported survival of babies ventilated for HMD has varied from 25% to 64% in our country². The lung epithelium of preterm infants is leakier than term infants, increasing the likelihood of protein passage on to the alveolar surface, where it inhibits surfactant function. Moreover preterm infants are more prone to asphyxia, hypothermia, hypoxia and hypotension, all of which impair surfactant synthesis or increase the leakiness of alveolar capillaries. Various other factors which influence the risk of HMD among preterm infants are discussed below.

Table 1.: Incidence of HMD by Gestational Age

Gestational Age	Incidence of HMD
501-750	86%
751-1,000	79%
1,001-1,250	48%
1,251-1,500	27%

The disease occurs more commonly in males than females and is more common in white than in non-white infants⁴ with an increased risk of death in males⁵. The delayed maturation of Lecithin Sphingomyelin ratio and the late appearance of phosphatidylglycerol⁶ which are androgen induced⁷ explain the increased incidence in males. The incidence of HMD in preterm African infants < 32 weeks GA has been shown to be 40% as compared to 75% in Caucasian preterm infants⁸. Allelic variation in the surfactant protein A gene has been reported between American whites and Nigerian blacks⁹. The incidence of HMD is higher for infants born by caesarean section without labor at any gestational age than infants delivered vaginally¹⁰. The timing of caesarean section is also important: the need for

mechanical ventilation being 120 times higher after elective cesarean section at 37 to 38 weeks as compared with 39-41 weeks¹⁰. When the effect of gestational age is removed, the occurrence of HMD is more in infants of mothers with gestational or insulin dependent diabetes. This is due to delay in the maturation of alveolar type II cells and decreased proportion of saturated phosphatidylcholine in the surfactant. Improvements in maternal diabetic control during pregnancy have now facilitated the delay in delivery until the 39th-40th week of gestation and HMD now occurs in < 1% of patients. Babies who are depressed at birth are at an increased risk of developing HMD, due to the ischemic damage to pulmonary capillaries as a result of fetal asphyxia leading to a leakage of protein fluid out of the damaged capillaries. This leakage of fluid leads to inactivation of the surfactant. Also, the hypoxemia and acidemia predispose to pulmonary hypertension and hypoperfusion, leading to a right to left shunt and reduction of surfactant synthesis by inhibition of synthetic enzymes. The contributions of genetic variations (polymorphisms and mutations) to the pathogenesis of HMD have been shown by molecular biology techniques. Congenital alveolar proteinosis, a disorder in which there is deficiency of Surfactant protein B resulting in lethal respiratory failure has been described in various families¹¹ and the inheritance is autosomal recessive. Partial deficiency of SP-B, which may be compatible with survival, has been reported. Other factors which contribute to occurrence and progression of HMD have been enumerated in Table 2.

Table 2.: Risk factors of HMD

Increased Risk	Decreased Risk
Prematurity	Chronic intra-uterine stress
Male Gender	Prolonged rupture of membranes
Familial predisposition	Maternal hypertension or toxemia
Cesarean section without labor	IUGR/SGA
Perinatal asphyxia	Antenatal glucocorticoids
Caucasian race	maternal use of narcotics/cocaine
Infant of diabetic mother	Tocolytic agents
Chorioamnionitis	Hemolytic disease of the newborn
Non-Immune hydrops fetalis	
Hypothyroidism	
Second of Twin	
Hypothermia	
Early clamping of cords	

Maternal conditions which compromise fetal growth may be associated with a decreased risk of HMD, and include pregnancy induced hypertension, chronic hypertension, sub acute placental abruption, narcotic addiction, smoking and alcohol ingestion. Heroin can mature surfactant synthesizing systems and the effect of cocaine is unclear.

PATHOLOGY

The lungs on autopsy are edematous, congested and are diffusely atelectatic. There is reduced distensibility and lungs are easily collapsible. The initial histological findings in non-treated neonates with HMD include alveolar epithelial cell necrosis which develops within 30 minutes after birth. The epithelial cells become detached from the basement membrane and small patches of hyaline membrane are formed on the denuded areas (Fig 1). The peripheral air spaces are collapsed, but more proximal respiratory bronchioles which are lined with necrotic epithelium and hyaline membranes are over distended. The hyaline membranes, composed of plasma exudation products and associated with damaged capillaries appear within 3 hours after birth¹². Hyaline membranes are eosinophilic on staining with haematoxylin and eosin and contain nuclear debris. Studies in

animals have shown neutrophil accumulation in the air spaces and capillaries within few hours, which may contribute to lung injury. Circulating neutrophil counts are lower in infants with HMD and the neutrophil count is inversely correlated with severity of HMD. The recovery phase is characterized by the regeneration of alveolar cells particularly type II cells with the resultant increase in surfactant activity.

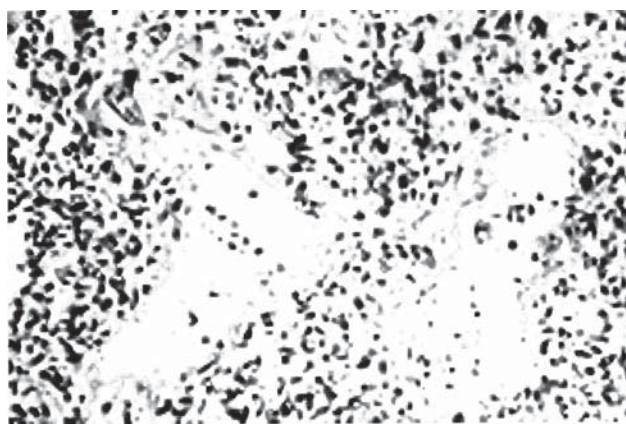


Fig. 2.: Histologic appearance of lungs in an infant with respiratory distress syndrome note the marked atelectasis and so called hyaline membranes lining the dilated alveolar ducts

PATHOPHYSIOLOGY

The lungs are non compliant initially with low functional residual capacity (FRC) which is the amount of air inside the lungs at end-expiration. Once surfactant begins to appear, the compliance improves and returns to values of 1-2 ml/cm/H₂O by 6 to 7 days of age. The functional residual capacity as analyzed by nitrogen washout may be decreased to 3 ml/kg in cases of severe disease, whereas it may be at a normal level of 25-30 ml/kg in recovering babies. Babies with HMD have a low tidal volume because of low FRC and to compensate, they have to increase their respiratory rate. However, the increase in minute ventilation due to an increase in respiratory rate is not sustained, resulting in alveolar underventilation and carbondioxide retention. Pressure - volume loops on lungs dying of HMD have a characteristic pattern¹³. There is a small increase in volume for a given increase in pressure during inflation and during deflation, the change in volume follows a track almost same as inflation, whereas in normal lungs there is retention of air until lower pressures are reached. As the pressure reaches zero, very little or no air is retained in the surfactant-less alveoli, corresponding to the low FRC measured in vivo. There is an increase in the expiratory resistance as a result of the closure of the airway prior to the expiratory grunt and also due to the presence of an endotracheal tube.

The time constant gives a measure of the time available for the gas to leave the lung during expiration, which is accepted to take 3 time constants. It is equal to the product of compliance and airway resistance.

$$T_c(0.1 \text{ sec}) = \text{Compliance (0.001L/cm H}_2\text{O)} \times \text{Resistance (100 cm H}_2\text{O/L/sec)}$$

It is markedly short in cases of severe HMD. In babies with less stiff lungs, the time constant will be longer, and if the baby breathes rapidly, this will result in gas being retained in his lungs when the next expiration starts.

Expiratory grunt occurs classically in babies with HMD as a result of baby attempting to sustain an FRC by delaying the escape of air from lungs during expiration. This occurs due to two mechanisms, firstly the diaphragm continues to contract during expiration, thus retaining gas within the alveoli and secondly, by contracting the constrictor muscles of the larynx, an attempt is made to close the upper airway as in Valsalva manoeuvre. Since the abdominal muscles contract at the same time as the laryngeal muscles relax, there is an explosive exhalation of air which is the characteristic grunt. The preterm infant is born with poor reserves of surfactant which gradually disappears and results in progressive deterioration as the neonate struggles to maintain ventilation in stiff, surfactant deficient lungs. The lungs become non-compliant and atelectatic until surfactant begins to appear from 36-48 hours of age. The leakage of proteins such as fibrin into the alveolar space further inactivates surfactant. Thus, the deficiency of the surfactant together with the decreased lung compliance leads to alveolar hypoventilation and ventilation perfusion (V/Q) mismatch. This mismatch represents the true intrapulmonary right to left shunt, when pulmonary capillary blood passes through the lung without coming into contact with a ventilated alveolus. Thus, the severity of hypoxemia in babies with HMD is directly related to the size of the open poorly ventilated compartment. The low V/Q ratio produces hypoxic vasoconstriction and there is alteration in the right to left shunt with changes in oxygen concentration. Right to left shunt may also occur across PDA and foramen ovale during the first 48-72 hours in babies with HMD in the presence of high pulmonary pressures. There is also increased carbon dioxide in arterial blood (PaCO₂) due to hypoventilation secondary to atelectasis, decreased tidal volume and decreased dead space. The relative role of surfactant deficiency and pulmonary hypo perfusion in the overall clinical picture of HMD vary somewhat with each patient. The natural history is invariably altered these days due to the often-combined use of exogenous surfactant therapy and mechanical ventilation (Fig 2).

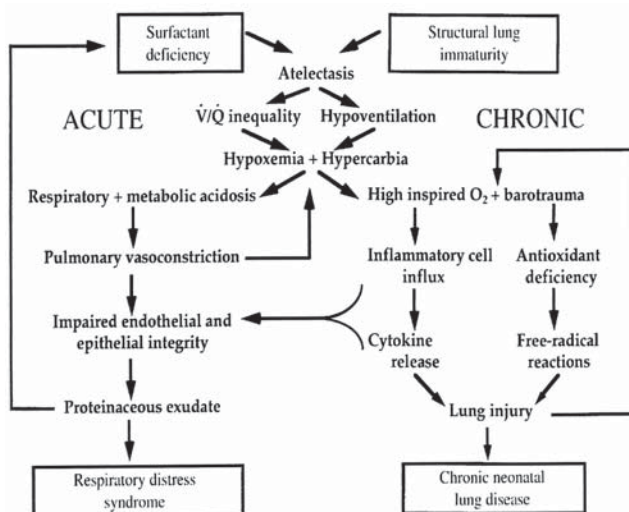


Fig. 2 Pathophysiology of Hyaline Membrane Disease
Schematic representation of the complex series of acute and chronic events that lead to neonatal respiratory distress syndrome and the accompanying lung injury secondary to therapeutic intervention in these infants

CLINICAL FEATURES

The neonate is almost always a preterm and symptoms usually appear within minutes after birth, although they may present several hours after birth. Prominent symptoms include rapid and labored breathing with a characteristic grunt, subcostal and intercostal retractions, oxygen requirement which gradually increases over 24-48 hours, nasal flaring, cyanosis and oliguria. Retractions are prominent and are due to the collapse of the compliant rib cage on inspiration as the infant tries to generate high inspiratory pressures to expand the poorly compliant lungs. Downe's score¹⁴ (Table 3) is used for monitoring the progress of respiratory symptoms in these babies. It consists of 5 components and each is assigned a score of 0, 1 or 2. A cumulative Downe's score of 4 and above indicates the need for ventilation. Additional clinical features include pallor due to anemia or peripheral vasoconstriction and hypotension. Hypotension is usually the result of hypoxia and acidaemia leading to decrease in the blood supply of various organs causing an increase in anaerobic metabolism, worsening acidosis, renal failure and NEC. The work of breathing progressively worsens over the next 24-36 hours in the absence of treatment with exogenous surfactant. Recovery usually starts by 3rd day of life with the onset of diuresis. Surfactant therapy greatly shortens the duration and severity of the disease. If the disease is severe enough, as is the case in extremely low birth weight infant, to require assisted ventilation or is complicated by the development of air leaks, significant shunting across PDA, recovery may be delayed by days to weeks. The presence of apneic episodes at an early stage of the disease is an ominous sign that could reflect thermal instability, electrolyte imbalance or sepsis but is often a sign of hypoxemia and respiratory failure.

Table 3.: Assessment of Downe's Score

Parameters assessed	0	1	2
Respiratory rate	<60/min	60-80/min	>80/min
Retractions	No retractions	Mild retractions	Moderate Retractions
Cyanosis	Nil	In room air	In FiO ₂ ≤0.4
Air Entry	Bilaterally equal	Decreased Unilaterally	Decreased or Absent Bilaterally
Grunting	No Grunting	Audible with stethoscope	Audible with naked ear



Fig. 3 Chest X-ray of a preterm neonate showing Air bronchogram

IMAGING STUDIES

Chest radiographs of a neonate with HMD shows bilateral diffuse reticular granular or ground-glass appearances, air bronchograms, and poor lung expansion (Fig 3). The prominent air bronchogram represent aerated bronchioles superimposed on a background of collapsed alveoli. The appearance can be very variable, from a slight

granularity to lungs that are so opaque that it is difficult to distinguish between lung and cardiac silhouette. Chest X ray appearance also depends upon the phase of the respiratory cycle, being worse during the expiratory phase. The cardiac silhouette may be normal or enlarged. Cardiomegaly may be the result of prenatal asphyxia, maternal diabetes, PDA, an associated congenital heart anomaly, or simply poor lung expansion. These findings may be altered with either early surfactant therapy or a PDA or with mechanical ventilation. The radiological findings of RDS cannot be differentiated reliably from those of pneumonia.

Echocardiographic evaluation is performed in selected infants to assist in diagnosing PDA and in determining the direction and degree of shunting on Doppler study. It is also useful in diagnosing pulmonary hypertension, assessing cardiac function, and excluding structural heart disease.

PREVENTION

The most effective way to decrease the incidence of HMD would be by preventing prematurity as HMD occurs predominantly in preterm neonates. This can be done by use of tocolytics, early diagnosis and treatment of infections and cervical cerclage. Presently the two major approaches for prevention include predicting risk of HMD by testing amniotic fluid, antenatal administration of glucocorticoids to accelerate fetal lung maturation and use of prophylactic surfactant at birth.

PRENATAL PREDICTION

Prenatal estimation of lecithin sphingomyelin ratio (L/S), phosphatidylglycerol (PG), surfactant proteins A and B, lamellar body counts and foam stability tests in amniotic fluid samples have been used to predict the occurrence of HMD. The L/S ratio reflects the secretory activity of the lung, which is greatly accelerated at 35 weeks. The incidence of HMD is only 0.5% for an L/S ratio of 2 or more but 100% for an L/S ratio of less than 1¹⁵. The presence of PG at 1% of total phospholipids indicates an extremely low risk for HMD. However, in certain pregnancies, characterized by diabetes and Rhesus isoimmunization, L/S ratio is not reliable¹⁶.

ANTENATAL GLUCOCORTICOIDS

ADMINISTRATION

Antenatal steroids cause induction of enzymes for surfactant synthesis and the genes for the production of surfactant proteins A, B, C and D. They also improve the quality of surfactant produced. Both dexamethasone and betamethasone have been used antenatally for prevention of HMD as they cross the placenta without being degraded. In 1972, Liggins and Howie published the results of the first randomized controlled trial (RCT) evaluating the effects of a single course of antenatal corticosteroids (ACS)¹⁷. In women who had been in spontaneous preterm labour, ACS reduced the risk of RDS and early neonatal mortality. Over the ensuing 20 years, multiple clinical investigations continued to document the effectiveness of ANCS on fetal lung maturation. Despite these findings, use of this therapy remained low in the United States (only 8.5% to 18% of women delivering preterm infants weighing <1,500 g), which prompted a 1994 NIH Consensus Development Conference on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes¹⁸ Table 4. The panel reviewed the results of clinical trials from 1972 to 1993. A meta-analysis of 15 published studies employing a single course of ANCS demonstrated consistent evidence of beneficial effects on neonatal outcome for infants born at less than 34 weeks' gestation¹⁹. There was a 50%

Table 4.: NIH Consensus Recommendations for the Use of Antenatal Corticosteroids

All fetuses between 24 and 34 weeks gestation at risk of preterm delivery should be considered candidates.
Administration should not be altered by fetal race or gender or by availability of surfactant therapy.
Patients eligible for therapy by tocolytics also should be eligible for treatment.
Treatment should be given unless immediate delivery is anticipated.
In preterm premature rupture of membranes at less than 30- 32 weeks gestation in the absence of clinical chorioamnionitis, treatment is recommended.
In complicated pregnancies where delivery prior to 34 weeks gestation is likely, treatment is recommended unless there is evidence that corticosteroids will have an adverse effect on the mother or the delivery is imminent.

reduction in overall incidence of RDS in the treated groups for infants born 24 hours to 7 days after treatment. In addition, there was a significant reduction in mortality (40%) and the development of intraventricular hemorrhage (IVH) (62%) among these infants. The data also indicated a reduction in RDS mortality and IVH among infants treated less than 24 hours before delivery. This resulted in NIH consensus panel recommendations which are highlighted in Table 4. A 2006 cochrane review of 2 RCTs involving more than 4269 infants, reports a reduced risk of neonatal death, RDS, and IVH with a single course of ACS, and a strong trend towards a reduced risk of abnormal neurodevelopmental outcome on long-term follow-up of the children.

Because approximately 50% of women given a course of ACS remain undelivered 7 to 14 days later, it has been suggested that women, who remain undelivered after a single course of ACS may benefit from receiving additional courses of ACS. Over recent years, several large clinical RCTs have been initiated to study the effects of repeat (weekly/biweekly) courses of ACS. If found to be beneficial in reducing serious neonatal morbidity, repeat courses of ACS will find their way into standard care in much less time than the twenty years that were required for single course ACS. In a study from India, it was found that a single course of antenatal betamethasone was as efficacious as multiple courses, with respect to prevention of neonatal morbidity²⁰. Multiple antenatal betamethasone courses had long-term adverse effects on infant weight and length growth, but not on OFC and neurodevelopment.

Treatment consists of two doses of betamethasone 12 mg given intramuscularly 24 hours apart or 4 doses of dexamethasone 6 mg given 12 hours apart. Meta-analysis of trials comparing betamethasone with dexamethasone revealed that although both agents decrease the frequency of RDS only betamethasone decreased neonatal mortality.

PROPHYLACTIC SURFACTANT

Human pulmonary surfactant consists of 90% lipids and 10% proteins. Surfactant has been studied for treatment of HMD since 1960s however the earliest successful use of surfactant in preterm neonates was reported by Fujiwara in 1980²¹. Surfactant can be used either prophylactically or as a treatment. A prophylactic, or preventive surfactant strategy is defined as intubation and surfactant administration to infants at high risk of developing respiratory distress syndrome for the primary purpose of giving surfactant rather than treatment of respiratory distress syndrome. This has been performed in clinical studies as surfactant administration before the onset of

respiratory symptoms or efforts, before initial resuscitation efforts, or, most commonly, after initial resuscitation but within 10 to 30 minutes after birth. This contrasts with a rescue surfactant strategy, in which surfactant is given to preterm infants with established respiratory distress syndrome. Rescue surfactant is most often administered within the first 12 hours after birth when specified threshold criteria for respiratory distress syndrome are met. Early rescue was defined as surfactant treatment within 1 to 2 hours of birth, and late rescue was defined as surfactant treatment 2 or more hours after birth. Cochrane database review published in 2001 concluded that prophylactic administration of natural surfactant resulted in a significant reduction in pneumothorax, mortality and the combined outcome of mortality and CLD in neonates less than 30 weeks of gestation²². The use of prophylactic surfactant for infants born at greater than 32 weeks of gestation would result in unnecessary treatment in a large number of infants particularly if the mother has received antenatal steroids.

MANAGEMENT

Management of infants with respiratory distress syndrome includes application of general supportive measures supplemented by surfactant treatment and measures of controlled assisted ventilation.

General supportive measures

These include appropriate resuscitation of preterm infants followed by transportation to the NICU in a thermo neutral environment. Early CPAP or surfactant should be considered in preterm infants depending upon the unit policy and all neonates who require intubation should be ventilated in the transport incubator. The infants should be nursed in a thermo neutral environment to maintain oxygen consumption at minimal levels. Monitoring of blood pressure, blood gases, electrolytes, calcium and glucose are needed in babies with HMD. These blood samples may be obtained by placing an umbilical arterial catheter. Appropriate attention should be made to the fluid and electrolyte status of the neonate guided by the change in baby’s weight and monitoring serum electrolyte status. Early administration of intravenous lipid and amino acids along with dextrose should be encouraged until an adequate intake of calories and protein is reached.

Surfactant Therapy

Surfactant given as early rescue therapy improves the outcome in babies with established RDS, resulting in reduction in pneumothorax, mortality and the combined outcome of mortality and BPD. Both natural and artificial surfactants are available and among natural surfactants bovine and porcine are commonly used. The various available surfactant preparations have been summarized in table 5. Surfactant-administration strategies have been based on manufacturer guidelines for individual surfactants. Type of surfactant, dose, frequency of administration, and treatment procedures have been modeled after research protocols (table 5). Furthermore, repeated doses of surfactants given at intervals for predetermined indications have decreased mortality and morbidity compared with placebo or single surfactant doses.

Surfactant has been administered through an endotracheal tube located in the trachea of infants either by bolus or infusion through an adaptor port on the proximal end of the endotracheal tube (Fig 4). Because data are conflicting and limited, the optimal method of surfactant administration in preterm infants has yet to be clearly proven although clinical experience and results of animal studies have shown that rapid instillation is more effective than slow

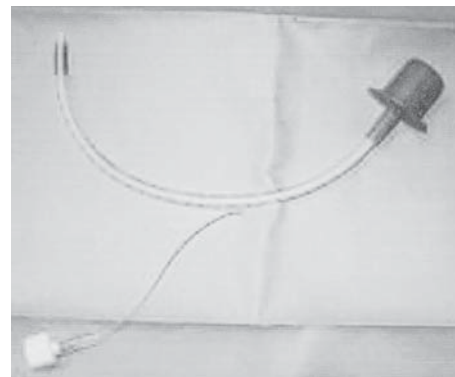


Fig. 4: Endotracheal tube with a side port for administering surfactant

Table 5.: Various surfactant preparations available in India

Name of Surfactant	Dose	Volume per vial	Content in mg per ml	Approximate Cost Rupees/vial
Survanta	4 ml/kg	8 ml	25	13000
Curosurf	2.5 ml/kg 1st dose repeat dose 1.25 ml/kg	2.5 ml	80	10000
Neosurf	5 ml/kg	3 ml 5 ml	27	3 ml vial 5000 5 ml vial 7000

instillation²³. Valls-i-Soler and colleagues showed that use of a dual lumen tube rather than disconnection from the ventilator led to fewer dosing problems²⁴. The surfactant usually disseminates homogeneously, particularly if large rather than small doses are used. There was no difference in clinical outcomes when 2 fractional doses of surfactant were given in 2 body positions compared with 4 fractional doses given in 4 positions²⁵. Aerosolized surfactant preparations and continuous positive airway pressure–aided delivery of pharyngeal surfactant theoretically could allow administration without intubation; these preparations and route of delivery have yet to be proven effective. Treatments with animal-derived surfactants have several advantages over first-generation protein- free synthetic surfactants. Some infants do not respond favorably to surfactant therapy. Factors that lead to an unfavorable response include the presence of PDA, cardiogenic shock or PPHN, air leaks and systemic hypotension. The need for a high oxygen concentration and ventilation pressures during the early stages of the disease have been identified as risk factors for an inadequate response.

Ventilation strategies

There is still uncertainty among clinicians whether the primary aim in the early hours of a preterm infant’s life should be to avoid intubation and provide support with nasal CPAP or to intubate electively to provide surfactant therapy before determining what other respiratory support is then appropriate. Whichever approach is preferred, many preterm infants require a period of artificial ventilation during their initial stabilization after birth. When ventilating preterm infants after birth, large volume lung inflations, as indicated by excessive chest wall movement, should be avoided. Although measured peak inflation pressure does not correlate well with volume delivered when respiratory mechanics are changing, monitoring of pressure may help to provide consistent inflations and to avoid unnecessarily high pressures. If positive-pressure ventilation is required during initial stabilization, an initial inflation pressure of

20 to 25 cm H₂O is adequate for most preterm infants. If a prompt improvement in heart rate or chest movement is not obtained, higher pressures may be needed. There is insufficient information about the value of PEEP during resuscitation. If ongoing ventilation is considered necessary, however, PEEP should be employed as soon as practicable. PEEP can be delivered in the labor room with T piece resuscitator till the baby can be shifted to transport incubator. Various devices are available for administration of PEEP which includes nasal prongs and masks (Fig 5) In the COIN trial published in 2008, it was seen that in infants born at 25-to-28-weeks' gestation, early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, as compared with intubation²⁶. Even though the CPAP group had more incidence of pneumothorax, fewer infants received oxygen at 28 days, and they had fewer days of ventilation.

KEY MESSAGES

1. Hyaline Membrane Disease is a disorder of preterm neonates
2. Presenting symptoms include tachypnea, retractions, grunting and increasing oxygen requirements occurring immediately or within few hours of birth
3. Antenatal treatment with glucocorticoids decreases the incidence and severity of the disease
4. Early surfactant therapy should be given as soon as possible in neonates with symptoms suggestive of the disease and prophylactically in neonates less than 28 weeks

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DRUG PROFILE

COLISTIMETHATE SODIUM

Mode of action: Colistimethate sodium is a cyclic polypeptide antibiotic derived from *Bacillus polymyxa* var. *Colistin* and belongs to the polymyxin group. Work by damaging the cell membrane and is selective for Gram-negative bacteria that have a hydrophobic outer membrane. Microbiology: Commonly susceptible species *Pseudomonas aeruginosa* acinetobacter species citrobacter species, *Escherichia coli* neisseria species proteus species anaerobes all gram-positive organisms. Pharmacokinetics: In healthy volunteers given a bolus injection of 150 mg (2 million units approx.), peak serum levels of 18 mg/L are observed 10 minutes after injection. When given by nebulisation, absorption is variable. Protein binding is low. The steady-state volume of distribution in cystic fibrosis patients is 0.09 L/kg. Colistimethate sodium undergoes conversion to its base (Colistin) in vivo. The main route of elimination after parenteral administration is by renal excretion with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours dose reduction is required in renal impairment to prevent accumulation. After intravenous administration to healthy adults, the elimination half-life is around 1.5 hours. In a study in a cystic fibrosis patients given a single 30-minute intravenous infusion, the elimination half-life was 3.4±1.4 hours.

Indications: Serious infections caused by Gram-negative bacteria by inhalation of *Pseudomonas aeruginosa* lung infection in patients with cystic fibrosis. **Dosage and method of administration:** The drug is given as a 50 ml intravenous infusion over a period of 30 minutes. Minimum of 5 days treatment is generally recommended. For the treatment should be continued for up to 12 days. **For the adult up to 60 kg :** 50,000 units/kg/day to a maximum of 75,000 units/kg/day. Given at approximately 8 hour intervals. For over 60 kg: subject 1-2 million units three times a day. The maximum dose is 6 million units in 24 hours. Serum level estimations are recommended impairment, neonates and cystic fibrosis patients. Levels of 10-15 mg/L colistimethate sodium should be adequate for most infections. For children <2

years: 500,000-1 million units twice daily, for children >2 years and adults: 1-2 million units twice daily. **Reconstitution for Inhalation** the required amount of powder is dissolved, preferably, in 2-4 mL of 0.9% sodium chloride solution and poured into the nebuliser. **CONTRAINDICATIONS :** In patients with known hypersensitivity to colistimethate sodium (colistin) or to polymyxin B and in patients with myasthenia gravis. **Drug Interactions:**

Table : Dosage Adjustment in Renal Impairment

Grade	Creatinine Clearance (mL/min)	Over 60 kg Bodyweight
Mild	20-50	1-2 million units every 8 hours
Moderate	10-20	1 million units every 12-18 hours
severe	<10	1 million units every 18-24 hours

Concomitant use of colistimethate sodium with aminoglycoside (increased risk of nephrotoxicity) neuromuscular blocking drugs and either colistimethate sodium crosses the placental barrier and hence should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus, the drug is secreted in breast milk.

Undesirable effects : Adverse events may be related to the age, renal function and condition of the patient. In cystic fibrosis patients, neurological events occur in up to 27% of patients. These patients treated with the recommended dosage limits, nephrotoxicity appears to be rare (less than 1%). Hypersensitivity reactions, including skin rash and drug fever, have been reported. Inhalation may induce coughing or bronchospasm.