Core Concepts: Meconium Aspiration Syndrome: Pathogenesis and Current Management

Tsu F. Yeh, MD, PhD*

Author Disclosure
Dr Yeh has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Abstract

Aspiration of meconium produces a syndrome characterized by hypoxia, hypercapnia, and acidosis. Perinatal hypoxia, acute airway obstruction, pulmonary inflammation, pulmonary vasoconstriction, pulmonary hypertension, and surfactant inactivation all play a role in the pathogenesis of meconium aspiration syndrome (MAS). Most aspiration of meconium probably occurs before birth. Following aspiration, meconium can migrate to the peripheral airway, leading to airway obstruction and subsequent lung inflammation and pulmonary hypertension. The presence of meconium in the endotracheal aspirate automatically establishes the diagnosis of meconium aspiration. MAS can be diagnosed in any infant born with meconium staining of amniotic fluid who develops respiratory distress at or shortly after birth and has positive radiographic findings. Prevention of intrauterine hypoxia, early cleaning (suctioning) of the airway, and prevention and treatment of pulmonary hypertension are essential in the management of MAS. Recent studies suggest that avoidance of postterm delivery may reduce the risk of intrauterine hypoxia and the incidence of MAS. Routine intrapartum naso- and oropharyngeal suction does not appear to affect the incidence and outcome of MAS. Endotracheal suction now is reserved only for infants who are depressed or have respiratory distress at birth. Mortality of MAS has improved; the causes of death are related primarily to hypoxic respiratory failure associated with irreversible pulmonary hypertension. Morbidity is affected mostly by perinatal hypoxia.

Objectives

After completing this article, readers should be able to:

1. Characterize meconium aspiration syndrome (MAS).
2. Explain the pathophysiology that occurs after meconium aspiration.
3. Review prevention measures and treatment of MAS.

Abbreviations

A-aDO_2:	alveolar-arterial oxygen gradient
ECMO:	extracorporeal membrane oxygenation
FRC:	functional residual capacity
HFOV:	high-frequency oscillatory ventilation
HFV:	high-frequency ventilation
iNO:	inhaled nitric oxide
MAS:	meconium aspiration syndrome
NO:	nitric oxide
OI:	oxygenation index
PDE:	phosphodiesterase
PEEP:	positive end-expiratory pressure
PPHN:	persistent pulmonary hypertension of the newborn
SIMV:	synchronized intermittent mandatory ventilation

Introduction

MAS in the newborn is characterized by hypoxia, hypercapnia, and acidosis. Although the pathophysiology of this syndrome is not completely understood, recent advances in management and respiratory care have decreased the mortality rate substantially. Perinatal hypoxia, airway obstruction shortly after birth, and significant pulmonary vasoconstriction and hypertension are the three major causes of mortality and morbidity. In this review, we focus on the pathogenesis, clinical manifestations, and current management of MAS.

Incidence of Meconium-stained Amniotic Fluid and MAS

The incidence of meconium-stained amniotic fluid and MAS varies between populations and depends on such factors as the socioeconomic status of the family, advances in prenatal care, accessibility to medical care, effective regionalization of perinatal care, and age of the mother at the birth of the first

*Chair and Professor of Pediatrics, China Medical University, Taichung, Taiwan; Senior Neonatologist, John Stroger Hospital of Cook County, Chicago, Ill.

child. In the United States, meconium-stained amniotic fluid occurs in as many as 10% to 15% of live births. The incidence of MAS decreased dramatically as the number of births occurring after 41 weeks' gestation was reduced. (1) In a prospective study of infants born after 37 weeks' gestation, MAS decreased from 5.8% to 1.5% during the period 1990 to 1997. (1) This was associated with a 33% reduction in births at more than 41 weeks' gestation.

Pathogenesis of MAS

Meconium Passage

Although the mechanisms of in utero passage of meconium are not understood completely, they depend on increased intestinal peristalsis, relaxation of the anal sphincter, and a gestational age greater than 34 to 35 weeks. Before 34 weeks' gestation, meconium usually is not in the descending colon and rectum. Increased peristalsis may be caused by increased concentrations of motilin (2) or triggered by infection, (3) hypoxia, or vagal stimulation produced by sporadic or repetitive cord compression, any of which also may result in sphincter dilation.

However, meconium may be passed spontaneously in a term or postterm fetus that has a mature gastrointestinal tract with no evidence of fetal distress or in babies who experience only transient or sporadic intrauterine stress with adequate cardiovascular compensation.

Characteristics of Human Meconium

Human meconium is a viscous and odorless substance consisting of water, lanugo, desquamated cells, vernix, amniotic fluid, pancreatic enzymes, and bile pigment. Meconium is a good medium for bacterial growth, particularly for gram-negative bacilli. Several constituents of meconium, especially free fatty acids and bile salts, may affect the surface tension of alveoli by displacement or inhibition of surfactant.

Mechanisms of Meconium Aspiration

Aspiration usually occurs in utero as a consequence of hypoxia-induced gasping. Most infants who have MAS (>60%) are born by cesarean section, indicating that they aspirate meconium before birth. Some aspiration may occur during the second stage of labor, when the shoulders and chest are delivered. It remains questionable, however, if there is a significant amount of meconium present in the oropharynx to cause MAS.

Pathophysiology After Aspiration of Meconium

Gooding and associates (4) demonstrated the immediate effects of meconium aspiration in an animal model (Fig. 1). Aspiration of a large amount of tenacious meconium led to acute cor pulmonale-induced heart failure and death. Aspiration of moderate amounts of meconium, however, was associated with a much better survival rate. Meconium may migrate gradually (within 1 to 2 hours) to the peripheral portions of the lungs. Acute cor pulmonale rarely is observed today in the clinical setting because infants usually undergo immediate resuscitation in the delivery room. However, meconium gradually migrates, either by spontaneous respiratory movements or by positive-pressure ventilation, to the small airways. Thus, endotracheal suction should be performed as early as possible if the infant has respiratory distress shortly after birth.

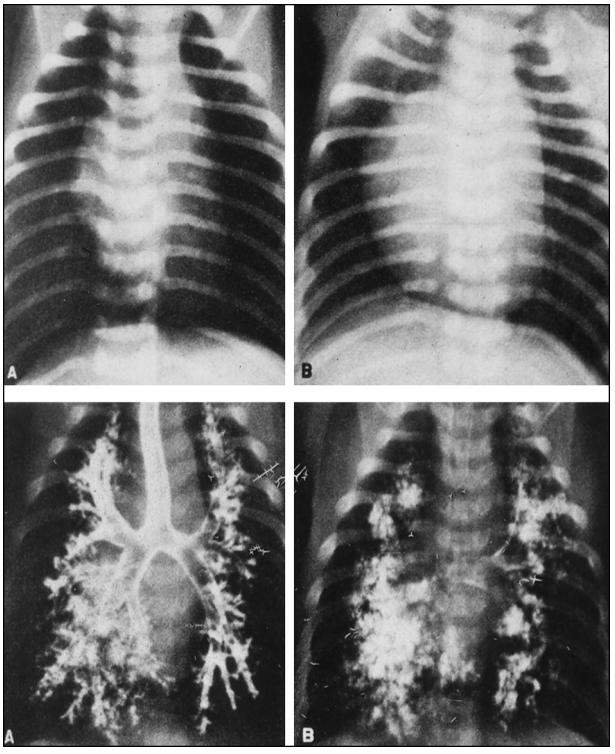

Figure 1. Upper A: Normal chest radiograph of newborn puppy before injection of meconium. Upper B. One minute after injection of 2 mL of 50% meconium into the trachea, the right atrium has become markedly dilated. The puppy died of acute cor pulmonale. Lower A. The injected tantalum-labeled meconium is distributed throughout the tracheobronchial tree. Lower B. One hour later, the tantalum-labeled meconium has been cleared from the trachea and mainstem bronchi, but material has also migrated peripherally. Reprinted with permission from Gooding CA, et al. (4)

After migration to the lower airway, meconium may block the airway, either partially or completely, leading to hyperaeration or atelectasis of the respiratory unit (Fig. 2). Meconium eventually is cleared from the lungs by macrophages (Fig. 3). During this stage, inflammation plays an important role in the pathophysiologic changes. MAS induces hypoxemia via five major effects: airway obstruction, pulmonary vasoconstriction and hypertension, surfactant dysfunction, infection, and possible chemical pneumonitis.

Airway Obstruction

The most prominent effect of meconium aspiration, particularly during the early course of the disease, is airway obstruction. Depending on the physical characteristics of meconium and the amount aspirated, meconium may partially or completely block the airway, leading to either hyperdistention or atelectasis of the alveoli. The gas that is trapped may rupture into the pleura, resulting in air leaks, namely, pulmonary interstitial emphysema, pneumomediastinum, and pneumothorax.

Pulmonary Vasoconstriction and Persistent Pulmonary Hypertension

Persistent pulmonary hypertension of the newborn (PPHN) frequently accompanies MAS, with right-to-left shunting caused by increased pulmonary vascular resistance. Two-dimensional echocardiography should be used to evaluate pulmonary hypertension during the course of the illness. Significant pulmonary hypertension with right-to-left shunting occurs in about 20% to 40% of infants who have MAS. PPHN in infants who have MAS could be due to: 1) hypertrophy or neomuscularization of post-acinar capillaries as a result of chronic intrauterine hypoxia; (5) 2) pulmonary vasoconstriction as a result of hypoxia, hypercarbia, or acidosis; or 3) pulmonary vasoconstriction as a result of lung inflammation.

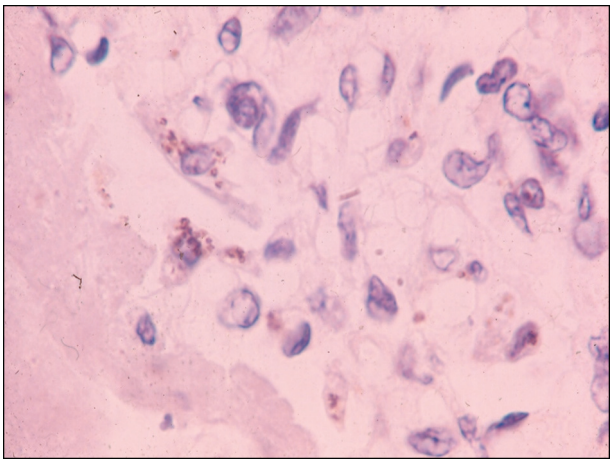

Figure 3. Meconium is usually picked up by macrophages 2 to 3 days after aspiration.

Chronic intrauterine hypoxia can induce muscle hypertrophy, causing thickening of the pulmonary vessels. PPHN usually presents in the subacute phase and as persistent hypoxemia at 6 to 24 hours after birth. In our study of MAS in newborn piglets, (6) we found that pulmonary arterial pressure was biphasic, with the early phase starting from 2 to 6 hours, possibly due to airway obstruction, and the later phase starting from 24 hours, possibly because of lung inflammation. A good positive correlation was seen between thromboxane B_2 and leukotriene D_4 in tracheal lavage fluids and mean pulmonary arterial pressure. The use of dexamethasone reduced the concentrations of thromboxane B_2 and 6-keto-prostaglandin-1-alpha and significantly improved cardiac stroke volume. (6)

Spontaneous recovery usually occurs within 3 to 4 days if the infant survives, suggesting that vascular constriction plays a role in the pathogenesis.

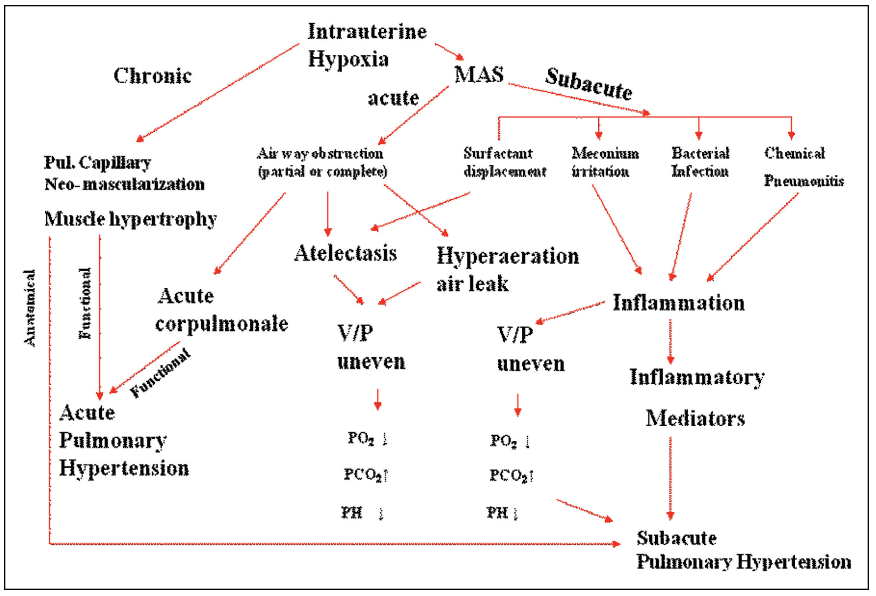

Figure 2. Pathogenesis of MAS. V/P=ventilation/perfusion.

Surfactant Dysfunction

Animal models of meconium aspiration have shown that meconium may inactivate surfactant function. Lung lavage fluid from infants who have MAS demonstrate higher-than-normal concentrations of surfactant inhibitors such as total protein, albumin, and membrane-derived phospholipids. Several constituents of meconium, especially the free fatty acids (eg, palmitic, stearic, and oleic acid), have a higher minimal surface tension than surfactant and may displace it from the alveolar surface, resulting in diffuse atelectasis, with decreased lung volume, compliance, and oxygenation. Bile salts in meconium may inhibit surfactant synthesis. The effect of MAS on surfactant dysfunction usually occurs in the subacute and late phase of the disease.

Infection

Meconium is a good medium for enhancing bacterial growth in vitro. Microscopic features characteristic of pneumonia frequently are seen at autopsy in affected infants treated with mechanical ventilation. However, a clinical study carried out by our group revealed that antibiotics are indicated only if there is a history of perinatal infection or if the infants have undergone vigorous resuscitation or are receiving mechanical ventilation. (7)

Chemical Pneumonitis

The pH of meconium is approximately 7.10 to 7.20. Aspiration of meconium may cause airway irritation. The enzymes and bile salts of meconium may cause a release of cytokines (eg, tumor necrosis factor-1-alpha and interleukins-1B, -6, -8, -13), which can result in diffuse toxic pneumonitis. Chemical pneumonitis has been demonstrated in an animal model, but the role that chemical pneumonitis plays in human MAS has not been clearly defined.

Pulmonary Function

The most prominent feature of MAS during the first 48 hours is high airway resistance. (8) Low compliance can be caused by atelectasis. The time constant is usually high during the first 3 days.

Lung volume, as measured by the closed-circuit helium dilution technique, can be low, normal, or high. The relationship between lung volume and compliance during the first 3 days is shown in Figure 4. Infants who have MAS may have low functional residual capacity (FRC) and low compliance, suggesting partial or complete atelectasis, or they may have high FRC and low compliance, suggesting overdistension of the lung. The

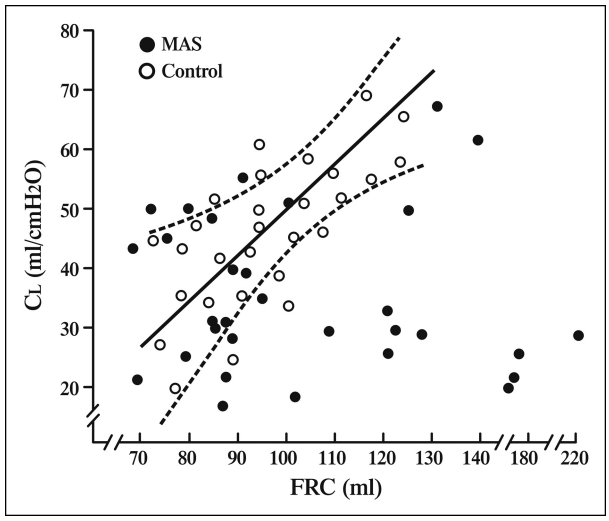

Figure 4. The relationship between lung compliance (C_L) and functional lung capacity (FRC) in healthy infants and infants who have MAS during the first 3 postnatal days. The solid line and dotted lines indicate mean and 95% confidence lines for healthy infants. The solid circles represent infants who have MAS. Infants who have MAS can either have high FRC and low C_L, indicating hyperaeration, or low FRC and low compliance, indicating atelectatic lung.

discrepancy between lung aeration and poor compliance also can be seen in the lung at different locations. Maldistribution of ventilation and aeration is common in MAS. Arterial blood gases show a low P_{O_2} and a high alveolar-arterial oxygen gradient (A-aDO_2) due to intrapulmonary shunting, uneven ventilation-perfusion ratio, or extrapulmonary shunting. Arterial P_{CO_2} usually is in the normal range or lower. Increased P_{CO_2} generally indicates an air leak or the presence of PPHN.

Because of the increase in airway resistance and consequently the time constant, adequate expiratory time should be permitted for exhalation to avoid adverse positive end-expiratory pressure (PEEP) during mechanical ventilation. Because of the abnormal air distribution and subsequent abnormal compliance in the lung, high-frequency oscillatory ventilation (HFOV) may be a better method of achieving good ventilation and oxygenation.

Diagnosis

Clinical Features

The diagnosis of MAS typically is based on the following criteria: 1) meconium-stained amniotic fluid or infant or both, 2) respiratory distress at birth or shortly after birth, and 3) positive radiographic features. If the infant re-

quires intubation, the presence of meconium in endotracheal suctioning automatically establishes the diagnosis.

Infants who have MAS may present with yellowish-green-stained fingernails, umbilical cord, and skin. Postmature infants may have evidence of peeling skin, long fingernails, and decreased vernix. Other findings of MAS may include tachypnea, retraction, grunting, and barrel-shaped chest. Auscultation reveals rales and rhonchi. Tricuspid regurgitation murmur with changing intensity over time may be audible in infants who have PPHN. Other clinical features associated with perinatal asphyxia also may be seen in infants who have MAS (Table).

Radiographic Features

Essentially, three major features can be seen in MAS: 1) diffuse or local linear or patchy infiltrates, 2) consolidation or atelectasis, and 3) hyperaeration with or without air leaks (Fig. 5). The classic radiologic findings in MAS are diffuse, coarse, patchy infiltrates that may alternate with areas of hyperexpansion. The lungs of infants who have severe MAS may show consolidation or atelectasis associated with hyperaeration, which most likely is due to aspiration of large, tenacious meconium particles. These features are predictive of poor outcome compared with features of generalized infiltration. (9) Radiographic changes may resolve within 7 to 10 days, although they can persist for weeks. Cardiomegaly may be seen in infants who have MAS, particularly when accompanied by pulmonary hypertension.

Table. Commonly Associated Findings With MAS

Cardiovascular Consequences of Asphyxia
• Hypoxemia-related pulmonary hypertension
• Hypoxemia-related myocardial dysfunction
Pulmonary Consequences of Asphyxia
• Decreased surfactant
• Pulmonary edema
• Meconium aspiration syndrome
Renal Consequences of Asphyxia
• Tubular and medullary necrosis
• Bladder paralysis
Central Nervous System Consequences of Asphyxia
• Hypoxic-ischemic encephalopathy
• Intracranial hemorrhage

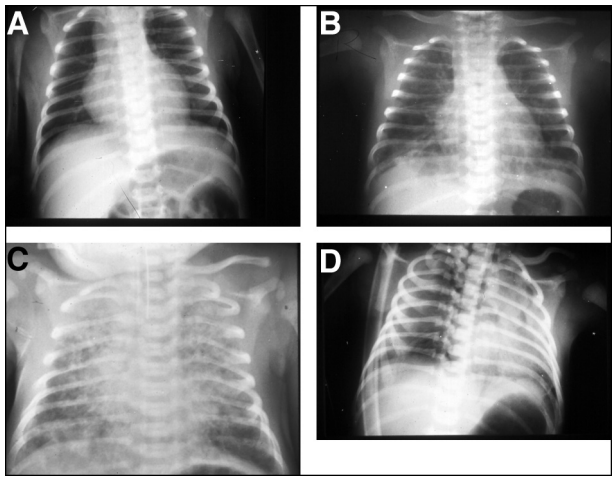

Figure 5. Chest radiographs of MAS. A. Mild linear infiltrates, usually indicating a small amount of thin meconium aspiration. B. Bilateral linear and patchy infiltrates, indicating a moderate amount of thin meconium aspiration. C. Bilateral generalized diffuse patchy infiltration, usually indicating a large amount of thin meconium aspiration. D. Partial left upper lobe atelectasis with hyperaeration of right lung, usually indicating large particles and thick meconium aspiration. The infant often develops respiratory failure and requires extensive respiratory therapy. Reprinted with permission from Yeh TF, et al. (9)

Management

Prepartum Prevention

The decreased incidence of MAS over the last decade has been attributed to the reduction in postterm delivery, aggressive management of abnormal fetal heart rate monitoring, and decreased number of infants who have low Apgar scores. Continuous electronic fetal monitoring is indicated for pregnancies that are complicated by meconium-stained amniotic fluid. Timely intervention should be initiated in the presence of a nonreassuring fetal heart rate tracing such as a category III tracing. Fetal pulse oximetry is a new modality for antepartum fetal surveillance, (1)(10)(11) but its effect on outcome remains questionable. Postterm delivery often is associated with intrauterine hypoxia and meconium-stained amniotic fluid, and, as noted previously, the reduction in postterm delivery has led to a reduction in the incidence of MAS. (10)

Amnioinfusion may be an effective therapy for pregnancies complicated by oligohydramnios and fetal distress. Amnioinfusion dilutes the thickness of meconium and may prevent umbilical cord compression and meconium aspiration. (12) However, studies have indicated that although this strategy decreases the amount of

meconium below the cords, in infants born to mothers who have meconium staining of amniotic fluid, it fails to reduce the risk of MAS. (13)(14) A recent multicenter study by Fraser and associates (15) concluded that amnioinfusion did not reduce the risk of moderate-to-severe MAS and MAS-related perinatal death in infants born through thick meconium. There is also insufficient evidence that amnioinfusion reduces meconium-related neonatal morbidity. Accordingly, amnioinfusion is not recommended for women who have meconium staining of amniotic fluid alone unless there is evidence of severe oligohydramnios and fetal distress. Because infection and chorioamnionitis may be associated with severe MAS, early administration of broad-spectrum antibiotic therapy in cases of maternal chorioamnionitis may reduce neonatal morbidity.

Intrapartum Prevention

Oropharyngeal and nasopharyngeal suction soon after delivery of the head but before the delivery of shoulders and chest has been a common practice in the past 2 decades that was shown to decrease the incidence and severity of MAS. (16)(17) However, a recent multicenter study showed that this strategy does not prevent MAS. (18) Researchers also showed that it does not reduce the mortality rate, the duration of ventilation and oxygen treatment, or the need for mechanical ventilation. Accordingly, such routine suctioning no longer is recommended, although it is recommended in specific cases, such as the presence of thick or copious meconium-stained fluid.

Postpartum Prevention

Endotracheal intubation and suction is performed to remove the meconium in the upper airway before it migrates to the lower airway. Meconium can migrate to the peripheral airway through spontaneous respiratory movement or positive-pressure ventilation. Therefore, it seems logical that endotracheal intubation and suction should be performed as early as possible after delivery, ie, before the baby takes the first breath or before active breathing. Until recently, routine intubation and tracheal suction was recommended for most infants who had meconium staining of amniotic fluid. (19) However, recent studies do not support universal aggressive suction unless the infant's respiration is depressed. Since 2005, the American Heart Association and the Neonatal Resuscitation Program have recommended tracheal suctioning only if the infant is not vigorous, has decreased muscle tone, or has a heart rate less than 100 beats/min.

Management of PPHN

Once the infant develops MAS, management is primarily supportive. Maintenance of adequate oxygenation; good systemic blood pressure; and correction of acidosis, hypoglycemia, or other metabolic disorders are the mainstays of treatment. The infant should be cared for in a neutral thermal environment and watched closely. Gentle care is essential; excessive handling and agitation should be avoided. An umbilical arterial catheter or radial arterial catheter should be inserted in infants who have moderate-to-severe MAS to monitor blood gases and blood pressure without disturbing the infant. We rarely use vasodilators for PPHN.

Infants who have MAS with low blood pressure may present with clinical features of PPHN. It is, therefore, important to maintain adequate systemic blood pressure in infants who have moderate-to-severe MAS. In addition to maintaining intravenous fluids, volume expanders such as normal saline and albumin are needed if patients have low blood pressure. Blood transfusion is indicated to keep hematocrit greater than 40% (0.40). Continuous intravenous infusions of dopamine (2 to 20 mcg/kg per minute), dobutamine (2 to 25 mcg/kg per minute), or epinephrine (0.01 to 0.03 mg/kg per minute) often are used separately or in combination. For infants who have intrauterine hypoxia and sustained hypotension, physiologic replacement with hydrocortisone may help overcome possible adrenal insufficiency and may stabilize the blood pressure. (20)(21)

Because hypoxia, acidosis, and hypercapnia may increase pulmonary vascular resistance, oxygen and ventilator therapy should be administered to maintain appropriate blood gas values and acid-base balance. Because infants who have PPHN are very labile during the acute phase of the disease, we prefer to maintain the arterial P_{O_2} near or above 100 mm Hg. Arterial blood gases should be monitored frequently and oxygen and ventilator support weaned gradually until the acute stage is over and the infant's condition stabilizes. We attempt to maintain the P_{CO_2} at 40 to 45 mm Hg and the pH around 7.35 to 7.45.

Early use of high-frequency ventilation (HFV), inhaled nitric oxide (iNO), or both may be needed to maintain appropriate blood gas values and acid-base balance. This approach may prevent the subsequent development of PPHN.

Patients who have PPHN are very sensitive to stimulation or excessive handling. Term infants may become agitated during intubation, and synchronization of the infant's breathing with mechanical ventilation may not be possible. Analgesia and anesthesia often are needed.

We prefer to begin with fentanyl at a dose of 1 to 5 mcg/kg per hour or midazolam at a dose of 10 to 60 mcg/kg per hour. An increased dose may be needed after several days of treatment because of the development of tolerance. Occasionally, a continuous intravenous infusion of morphine 100 to 150 mcg/kg over 1 hour followed by 10 to 20 mcg/kg per hour may be given. Muscle relaxants such as pancuronium 0.1 mg/kg per dose can be provided for unsynchronized ventilation but rarely are needed.

Ventilator Management

Approximately 30% of infants who have MAS require ventilator support. Such infants tend to breathe on their own, so some degree of sedation may be necessary. Airway obstruction and a prolonged time constant are the major features during the early course of the disease, which necessitates an adequate expiration time during the expiratory phase. (8) For this reason, caution should be taken to avoid increasing the inspiration time or reversing the inspiratory-to-expiratory ratio during mechanical ventilation. For similar reasons, during HFV, the rate should be kept below 15 Hz, if possible. This strategy may prevent adverse PEEP and air leaks. HFV is probably most appropriate to achieve good pulmonary ventilation and gas exchange in MAS. Clinical trials have shown that HFV reduces the need for extracorporeal membrane oxygenation (ECMO) treatment and decreases the incidence of air leaks in infants who have PPHN. We initially use synchronized intermittent mandatory ventilation (SIMV). If infants require high positive inspiratory pressure or high Fio_2 or are at a risk of developing air leak, we switch to HFOV. We allow crossover treatment because some babies respond differently. Clark and associates (22) showed that among patients who had severe respiratory disease, 63% who failed SIMV responded to HFOV.

Surfactant Therapy

Surfactant can be administered as bolus or as lavage. In a randomized, controlled study, Findlay and colleagues (23) concluded that surfactant replacement with three doses of 150 mg/kg (6 mL/kg) within 6 hours after birth improved oxygenation and reduced the incidence of air leaks, the severity of pulmonary morbidity, the need for ECMO treatment, and duration of hospitalization. Other studies have shown similar findings. Acute adverse effects of surfactant therapy include transient oxygen desaturation and endotracheal tube obstruction occurring during bolus administration. The dose of surfactant administered by bolus or slow infusion is not defined. We administer 100 mg/kg to infants who have severe MAS via an intratracheal indwelling catheter through the side hole of an endotracheal tube.

There is no evidence that surfactant therapy influences the mortality rate of infants who have MAS. The use of surfactant to lavage the airway may be more effective than single surfactant instillation, although no controlled study has been performed in neonates. It is reasonable to assume that surfactant therapy would be more effective after airway obstruction has been relieved.

Nitric Oxide Therapy

Nitric oxide (NO) is a potent vasodilator. iNO can be delivered to the alveoli through a ventilator, resulting in selective pulmonary vasodilatation. Once in the bloodstream, NO is metabolized by hemoglobin and, thus, has limited systemic effects. In general, iNO (20 ppm) is initiated when the oxygenation index (OI) exceeds 25. Although brief exposure to higher doses (40 to 80 ppm) appears to be safe, sustained treatment with 80 ppm iNO increases the risk of methemoglobinemia. The lowest effective initial dose of iNO in term newborns who have PPHN has not been determined, but sustained improvement in oxygenation has been demonstrated with doses lower than 10 ppm. (24)(25)

Methemoglobin and nitrogen dioxide concentrations should be monitored for 4 to 12 hours. Serial echocardiography is useful in monitoring the pressure gradients and myocardial function. Patients usually are maintained on low-dose iNO (5 to 20 ppm) for 2 to 6 days, then gradually weaned to avoid rebound hypoxemia. The combination of HFOV and iNO therapy can be more successful than treatment with HFOV or iNO alone in patients who have PPHN and respiratory distress syndrome or MAS as the underlying disease. (26)(27)

Steroids

Steroids are used in the treatment of MAS for several reasons: 1) they can stabilize the blood pressure, particularly in infants who suffer from intrauterine hypoxia and adrenal insufficiency; 2) they can inhibit chemical pneumonitis; 3) they can inhibit inflammation and decrease cytokine-induced vasoconstriction, and, therefore, may be beneficial for infants who have PPHN; and 4) dexamethasone can increase cardiac stroke volume and improve overall cardiopulmonary function. A double-blind trial of hydrocortisone use, however, did not show a beneficial effect. (28) Hydrocortisone may be useful for infants who have unstable blood pressure. The anti-inflammatory effect of dexamethasone in the treatment or prevention of PPHN has not been studied.

Phosphodiesterase (PDE) Inhibitors: Sildenafil and Milrinone

Sildenafil inhibits cGMP-specific PDE type 5, increases cGMP concentrations, and may result in pulmonary vasodilation or the enhancement of NO activity. Because PDE5 is primarily distributed within the arterial wall smooth muscle of the lungs and penis, sildenafil acts selectively in both these areas without inducing vasodilation in other areas of the body. Sildenafil is only available in enteral form. The drug was approved by the United States Food and Drug Administration for the treatment of pulmonary hypertension in adults, but data are limited in neonates. Baquero and associates (29) reported that oral sildenafil improves the OI in infants who have severe PPHN. The recommended dose is 0.3 to 1 mg/kg via orogastric tube every 6 to 12 hours. Potential adverse effects include worsening of oxygenation, systemic hypotension, and bleeding tendency. Milrinone is a specific PDE3 inhibitor that increases cAMP concentrations and decreases pulmonary vascular resistance.

Extracorporeal Membrane Oxygenation

The use of adjunctive therapies has dramatically decreased the need for ECMO therapy, (30) but some infants who have MAS and PPHN still develop persistent respiratory failure despite optimal medical treatments. (22) ECMO provides cardiopulmonary support while allowing the underlying pulmonary or cardiac dysfunction to resolve without the risk of further injury from barotrauma or hyperoxia. ECMO treatment increases the survival rate of infants who have MAS and PPHN from 80% to 94%.

The selection criteria for ECMO include: 1) more than 34 weeks' gestation, 2) birthweight more than 2,000 g, 3) lack of major coagulopathy or active bleeding, 4) no major intracranial bleeding, 5) mechanical ventilation of less than 10 to 14 days' duration and reversible lung disease, 6) failure of optimal medical management, and 7) infants who have a high predicted mortality rate.

OI and A-aDO^2 are used commonly to predict the likelihood of mortality. A mortality rate of 80% is associated with an OI of 40 or greater, an A-aDO$_2$ greater than 600 mm Hg, or both.

Potential Therapy for PPHN

A number of vasodilators are under investigation, including calcium channel blockers (nifedipine, diltiazem, verapamil), prostacyclin analogs (epoprostenol, treprostinil, iloprost), and endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan).

Outcome of MAS

The mortality rate associated with MAS-related illness has declined markedly over the past few decades: 4.2% during 1973 to 1987 in the United States to 2.5% during 1995 to 2002 in Australia and New Zealand. (1)(10) Perinatal deaths are related to perinatal depression (asphyxia), airway obstruction, and development of PPHN.

Pulmonary sequelae are common among infants who have severe MAS. Nearly 50% of all affected infants develop reactive airway diseases during the first 6 months after birth. Mild airway obstruction or exercise-induced asthma often present in the children at 6 to 8 years of age (31)(32)

The long-term neurologic outcomes of infants who have MAS depend on the underlying disorders. The neurologic outcomes are related to the presence or absence of intrauterine asphyxia, hypoxic-ischemic encephalopathy, and PPHN. Infants who require ECMO treatment tend to have more complications than infants who do not.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the significance and obstetrical management of meconium-stained amniotic fluid.
- Know the current recommendations regarding suctioning meconium from the airway during and following delivery.
- Know the pathogenesis, pathophysiology, pathologic features, and risk factors of meconium aspiration syndrome.
- Know how to manage meconium aspiration syndrome.
- Know the clinical, laboratory, and imaging features of meconium aspiration syndrome.
- Know the management of persistent pulmonary hypertension, including assisted ventilation, pharmacologic approaches, and ECMO.

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NeoReviews Quiz

10. The incidence of meconium aspiration syndrome (MAS) decreased from 5.8% to 1.5% of births from 1990 through 1997, as reported by Yoder and associates. Of the following, this decline in the incidence of MAS is *most* attributed to the:

    A. Enhancement of prenatal counseling.
    B. Implementation of regionalized perinatal care.
    C. Improvement in socioeconomic status of the families.
    D. Increase in access to cesarean section deliveries.
    E. Reduction in births past 41 weeks' gestation.

11. Meconium aspiration syndrome induces hypoxemia by several pathophysiologic effects of the aspirated meconium. Of the following, the *most* prominent effect of aspirated meconium, especially during the early course of the disease, is:

    A. Airway obstruction.
    B. Chemical pneumonitis.
    C. Nosocomial infection.
    D. Pulmonary vasoconstriction.
    E. Surfactant dysfunction.