ABSTRACT

Aspiration of meconium produces a syndrome (Meconium Aspiration Syndrome MAS) 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 MAS. Most aspiration of meconium probably occurs before birth. Following aspiration, meconium may migrate to the peripheral airway, usually take about 2 hours as demonstrated in animal experiment, leading to airway obstruction and subsequent lung inflammation and pulmonary hypertension. The presence of meconium in the endotracheal aspirate automatically establishes the diagnosis of MAS. Clinical diagnosis can be made 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 post-term 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 at birth is considered a controversial procedure and only reserved for infants who have severe retraction at birth suggesting an upper airway obstruction. High frequency oscillatory ventilation with nitric oxide or surfactant may improve mortality. 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.

Key Words: Meconium, Neonate, Aspiration

INTRODUCTION

Meconium aspiration syndrome (MAS) is characterized by hypoxia, hypercapnia, and acidosis1. Meconium aspiration occurs in 0.5% of all live births in the United States2. The first event of MAS is passage of meconium, which is probably a result of intrauterine
hypothesis. Following aspiration, meconium can migrate to the peripheral airway, leading to airway obstruction and subsequent lung inflammation and pulmonary hypertension. Prevention of intrauterine hypoxia, early cleaning of the airway, and prevention and treatment of pulmonary hypertension are essential in the management of MAS. The mortality rate has improved; Causes of death are primarily related to hypoxic respiratory failure, which is associated with irreversible pulmonary hypertension. Morbidity is affected mostly by perinatal hypoxia. Two review articles addressing the pathogenesis and current management of MAS in detail have been published by our group. The present report provides updates on the current management of MAS, focusing on airway management during resuscitation.

**MECONIUM PASSAGE**

Meconium passage from the fetus into the amniotic fluid is a result of peristalsis, tonic contractions of the anal sphincter, and a passage of thick and viscous meconium. Intestinal peristalsis is caused by several factors, one of which is higher motilin levels. Passage of meconium may occur naturally in a term or post-term fetus with a mature gastrointestinal tract without fetal distress. It may also be caused by spontaneous intestinal motility or bowel stimulation caused by infection or hypoxia. Passage of meconium into the amniotic fluid may also increase the risk of infection in the fetus. Vagal stimulation produced by sporadic or repetitive cord compression may be associated with passage of meconium into the amniotic fluid.

**CHARACTERISTICS OF HUMAN MECONIUM**

Human meconium is a viscous, odorless substance with a pH of 7.10–7.20. It is black or yellowish-green in color and is composed of desquamated epithelial cells, lanugo, vernix, and intestinal secretions including bile acid and bile pigment. Water is the major liquid constituent, comprising 80% of meconium. Meconium contains blood group-specific glycoproteins and small amounts of lipids and proteins that diminishes during gestation. Meconium may enhance bacterial growth. Several constituents of meconium, especially the fatty acids and bile acid, can either displace surfactant or inhibit it, resulting in diffuse atelectasis.

**MECHANISM OF MECONIUM ASPIRATION**

Aspiration usually occurs in utero as a consequence of hypoxia-induced gasping. Many infants who have MAS 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. However, it remains questionable whether the amount of meconium present

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**Figure 1.** Pathogenesis of meconium aspiration syndrome (MAS).
in the oro or nasopharynx is significant enough to cause MAS during the second stage of labor. Meconium may be aspirated after birth because of vomiting secondary to birth asphyxia.

**PATHOPHYSIOLOGY AFTER ASPIRATION OF MECONIUM (Figure 1)**

### Airway obstruction

The thick, viscid meconium can result in partial or complete airway obstruction. Partial obstruction causes air trapping and hyper-distension of the distal airway, commonly termed the ball-valve effect. The gas that is trapped may rupture into the pleura resulting in air leaks.

### Surfactant dysfunction

Animal models of meconium aspiration have shown that meconium results in the inactivation of surfactant, increasing the surface tension. Lung lavage fluid in infants with MAS demonstrated higher concentrations of surfactant inhibitors (total proteins, albumin, membrane-derived phospholipids). Several constituents of meconium, especially the free fatty acids (e.g., palmitic, stearic, oleic), have a higher minimal surface tension than surfactant and displace it from the alveolar surface, resulting in diffuse atelectasis and decreased lung volume, compliance, and oxygenation.

### Chemical pneumonitis

Enzymes, bile salts, and fats in meconium irritate the airways and parenchyma, causing a release of cytokines (including tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, IL-8, IL-13), which can result in a diffuse toxic pneumonitis that may begin within a few hours of aspiration. Finally, although meconium is sterile, its presence in the air passages can predispose the infant to pulmonary infection.

All of these pulmonary effects can produce gross ventilation-perfusion (V/Q) mismatch, which can result in hypoxemia, acidosis, and pulmonary hypertension. Meconium and its constituents may result in direct injury to the cord vessels and amniotic membranes and may also cause vasoconstriction of the placental and cord vessels.

### Abnormal pulmonary functions

Infants with MAS typically have high airway resistance, which is the most prominent feature during the first 48 hrs. Low compliance could either be due to over-inflation or partially atelectatic terminal respiratory units. Figure 2 sketches the terminal unit of the lung following meconium aspiration with different sizes of airway and alveoli, resulting in different resistance and compliance and a different time constant of each terminal unit.

Lung volume (functional residual capacity as measured by the closed system helium dilution technique) could be low or normal. Arterial blood gases usually show a low partial pressure of oxygen (PO\(_2\)), but normal or even low partial pressure of carbon dioxide (PCO\(_2\)), unless there is an air-leak. Infants with severe MAS may show hypoxemia and hypercarbia.

### Persistent pulmonary hypertension or hypoxic respiratory failure

Persistent pulmonary hypertension (PPHN) or hypoxic respiratory failure frequently accompanies a right to left shunt caused by increased pulmonary vascular resistance. A two-dimensional echocardiogram is used to evaluate pulmonary hypertension early in the course. PPHN may occur in 20-40% of infants with MAS. Many infants with MAS may have primary or secondary PPHN as a result of chronic intrauterine hypoxia, pulmonary capillary muscular hypertrophy, and thickening of the pulmonary vessels.

This condition usually presents as persistent hypoxemia at 6-24 hrs after birth. In a newborn piglet model, elevation of...
present with signs of encephalopathy. The associated clinical findings in MAS are shown in Table 1.

Radiologic features

The diagnosis of MAS is confirmed by a chest radiograph. The classic radiologic findings in MAS are diffuse coarse patchy infiltrates that may alternate with areas of expansion. In infants with severe MAS, the lungs may develop the appearance of homogeneous density similar to either consolidation or atelectasis. A series of 80 cases showed that MAS with consolidation or atelectasis was most predictive of poor outcome as compared to those without atelectasis or consolidation.

As the disease progresses, the lungs typically appear hyper-inflated with flattening of the diaphragm. Pneumothorax, pneumomediastinum, or pulmonary interstitial emphysema may be present in 15–33% of the infants. Pleural effusions are not uncommon. Radiologic changes resolve within 7–10 days; however, in some infants they may persist for several weeks.

MANAGEMENT

Prepartum prevention

The decreased incidence of MAS over the last decade has been attributed to a reduction in post-term delivery, aggressive management of abnormal fetal heart rate monitoring, and a 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 non-reassuring fetal heart rate tracing such as a category III tracing. Fetal pulse oximetry is a new modality for antepartum fetal surveillance, but its effect on outcome remains questionable. Amnioinfusion may be an effective therapy for pregnancies complicated by meconium-stained amniotic fluid. Timely intervention should be initiated in the presence of a non-reassuring fetal heart rate tracing such as a category III tracing. Fetal pulse oximetry is a new modality for antepartum fetal surveillance, but its effect on outcome remains questionable. Amnioinfusion may be an effective therapy for pregnancies complicated by meconium-stained amniotic fluid.

PPHN in infants with MAS could be due to:
1) Hypertrophy or neo-muscularization of post-acinar capillaries as a result of chronic intrauterine hypoxia
2) Functional pulmonary vasoconstriction as a result of hypoxia, hypercarbia, or acidosis, or
3) Functional pulmonary vasoconstriction as a result of lung inflammation.

Table 1. Cardiovascular, Pulmonary, Renal, and Central Nervous System Cardiovascular Consequences of Asphyxia

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pulmonary arterial pressure appeared to be biphasic, early phase starting from 2-6 hrs and late phase at 48 hrs. A strong positive correlation was observed between tracheal aspirate thromboxane B2 (TXB2), leukotriene D4, and mean pulmonary arterial pressure. The use of dexamethasone may reduce tracheal aspirate TXB2, and Keto-prostaglandin F1α. Spontaneous recovery usually occurs within 3-4 days if the patient survives, indicating that functional vascular constriction may play an important role in PPHN in most infants with MAS.

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DIAGNOSIS

Clinical features

MAS must be considered in any infant with a history of meconium staining of the amniotic fluid and development of respiratory distress. Infants with MAS may also present with yellow-green staining of fingernails, umbilical cord, and skin. Post-mature infants may have evidence of peeling skin, long fingernails, and decreased vernix. Infants with respiratory distress present with tachypnea, intercostal retractions, grunting, and barrel-shaped chest in the presence of air trapping. Auscultation reveals rales and rhonchi. Hypoxic infants may

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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 may reduce neonatal morbidity.

**Intrapartum prevention**

Oropharyngeal and nasopharyngeal suction soon after delivery of the head but before the delivery of shoulder and chest has been a common practice in the past 2 decades that has shown to decrease the incidence and severity of MAS. However, a recent multicenter study showed that this strategy does not prevent MAS. 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, except in specific cases such as the presence of thick or copious meconium-stained fluid. We believe that the functional space of the naso-oropharynx during the process of passing through the birth canal is probably very small and meconium remaining in this space is probably very minimal. Therefore, intrapartum suction may not have much effect on the morbidity rate of MAS.

**Postpartum prevention**

Endotracheal intubation and suction are performed to remove the meconium in the upper airway before it migrates to the lower airway. It has been shown that meconium can migrate to the peripheral airway through spontaneous respiratory movement or positive-pressure ventilation in 1–2 hours in an animal model. Therefore, it seems logical that endotracheal intubation and suction should be performed as early as possible after delivery, or within 2 hours before meconium migration to the peripheral airways. Until recently, routine intubation and tracheal suction were recommended for most infants who had meconium staining of the amniotic fluid. However, recent studies do not support universal aggressive suction unless the infant’s respiration is depressed. Since 2005, the American Heart Association (AHA) and the Neonatal Resuscitation Program (NRP) 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. Moreover, in the revised American Academy of Pediatrics (AAP), American Heart Association (AHA), and NRP guidelines (2015), routine tracheal suction in non-vigorous infants stained with meconium is no longer recommended. However, our suggestions are slightly different from what was recommended by the AHA Resuscitation Program. We feel that all pediatricians should be well trained and able to do endotracheal intubation at the delivery. We believe that infants who aspirate meconium and the presence of meconium in the upper airway, as shown by retraction and respiration distress, should undergo endotracheal intubation and suction as early as possible because once meconium has migrated to the lower airway, endotracheal suction becomes difficult. In such cases, subsequent chest physiotherapy (CPT) with warm and humid oxygen may be helpful in removing meconium from the lungs. Endotracheal suction can be easily done with endotracheal intubation or with a catheter if the doctor is familiar with this technique in the delivery room.

**Management of PPHN or hypoxic respiratory failure**

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 into infants who have moderate-to-severe MAS to monitor blood gases and blood pressure without disturbing the infant.

Infants who have MAS with low blood pressure may present with the clinical features of PPHN. Therefore, it is important to maintain an 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 required if patients have low blood pressure. Blood transfusion is indicated to maintain hematocrit greater than 40%. Continuous intravenous infusions of dopamine (2–20 mcg/kg per min), dobutamine (2–25 mcg/kg per min), or epinephrine (0.01–0.03 mg/kg per min) are often used separately or in combination. For infants who have intrauterine hypoxia and sustained hypotension, physiological replacement with hydrocortisone may help overcome possible adrenal insufficiency and may stabilize blood pressure.

Because hypoxia, acidosis, and hypercapnia may increase pulmonary vascular resistance, oxygen and ventilator therapy should be administered to maintain appropriate blood gas.
values and an acid-base balance. Infants who have PPHN are very labile during the acute phase of the disease, thus we prefer to maintain the arterial PO2 near or between 100–150 mmHg. 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 PCO2 at 40–45 mmHg and the pH around 7.35–7.45.

Early use of high-frequency oscillation ventilation (HFOV), inhaled nitric oxide (iNO), or both may be needed to maintain the 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 are often needed. We prefer to begin with fentanyl at a dose of 1–5 mcg/kg per hour or midazolam at a dose of 10–60 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 at 100–150 mcg/kg over 1 hr followed by 10–20 mcg/kg per hr may be given. Muscle relaxants such as pancuronium at 0.1 mg/kg per dose can be provided for unsynchronized ventilation, although this is rarely required.

Antibiotics

Meconium is a good media for bacterial growth; therefore, bacterial infection may associate with MAS and judicious use of antibiotics is indicated. Indeed, bacterial pneumonia is indistinguishable radiographically from MAS. Antibiotics are particularly needed if there is a perinatal history of infection or if the infant is intubated on mechanical ventilation.

Ventilator therapy

Conventional ventilator

Some alveoli in MAS are atelectatic and some are over-distended, thus resulting in V/Q mismatching. Approximately 30% of infants with MAS require ventilator support. These infants tend to breathe on their own to some degree. Compared with non-synchronized ventilation, infants treated with patient-triggered ventilation (synchronized intermittent mandatory ventilator [SIMV], and assist control ventilation [ACV]) required less sedation and were associated with a shorter duration of mechanical ventilation. There is limited experience with the other two new modes of ventilation; pressure regulated volume control ventilation (PRVCV) and SIMV plus pressure support PS.

High frequency oscillator ventilation (HFOV)

Because of the different time constant of each terminal respiratory unit following meconium aspiration, HFOV is probably the best choice for MAS to maintain the blood gases and an acid-base balance. HFOV uses low pressure and high frequency to recruit the collapsed alveoli, and delivers a more homogenous pulmonary ventilation and gas exchange. Clinical trials have shown that HFOV reduced the need for extracorporeal membrane oxygenation (ECMO) treatment and decreased air-leak in infants with PPHN. There are two types of high frequency ventilators available now in the United States: the Bunnel Life Pulse high-frequency jet ventilator (HFJV) and the SensorMedics high-frequency oscillatory ventilator (HFOV). The Infant Star was withdrawn from the market recently. HFOV can be used as a primary mode of ventilator therapy or as rescue therapy when patients fail to respond to a conventional ventilator. We use an intermittent mandatory ventilator (IMV) initially; however, if infants require a high peak inspiratory pressure (PIP), high fraction of inspired oxygen (FiO2), or are at a risk of developing an air leak, we switch to HFOV. We allow cross-over treatment since some babies respond differently from time to time. Clark et al. showed that among patients with severe respiratory disease, 63% who failed continuous mandatory ventilation (CMV) responded to HFOV; and 23% vice versa. HFOV can be used with nitric oxide (NO) or with surfactant, and can achieve a high success rate.

Surfactant therapy

Surfactant can be administered as a bolus or as lavage. In a randomized, controlled study, Findlay and colleagues concluded that surfactant replacement with three doses of 150 mg/kg (6 mL/kg) within 6 hrs of birth improved oxygenation and reduced the incidence of air leaks, the severity of pulmonary morbidity, the need for ECMO treatment, and the 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. The combined use of HFOV and surfactant may achieve a better result.

Inhaled nitric oxide (iNO)\(^{28-31}\)

Nitric oxide is a potent vasodilator. iNO can be delivered to the alveoli and reaches the vascular bed through a ventilator, resulting in selective pulmonary vasodilatation. Once in the bloodstream, NO is metabolized by hemoglobin; thus, it has limited systemic effects. In general, iNO is initiated when the oxygen index (OI) exceeds 25 and the starting dose is at 20 ppm. Although brief exposures to higher doses (40–80 ppm) appear to be safe, sustained treatment with 80 ppm iNO increases the risk of methemoglobinemia. The lowest effective initial dose for iNO in term newborns who have PPHN has not been determined, but sustained improvement in oxygenation has been demonstrated for doses lower than 10 ppm\(^ {28,29}\). Methemoglobin and nitrogen dioxide concentration should be monitored every 4–12 hrs. Serial echocardiograms are useful in monitoring the pressure gradients and myocardial functions in these infants. Patients are usually maintained on a low dose of iNO (5–20 ppm) for 2–6 days, and then gradually weaned to avoid rebound hypoxemia.

The OI is calculated as: OI = (mean airway pressure) × FiO\(_2\) × 100/post-ductal PaO\(_2\).

Initiating iNO treatment early at an OI greater than 15 did not change the incidence of ECMO requirement, death, length of hospital stay, duration of mechanical ventilation, or incidence of chronic lung disease\(^ {35}\).

Combination of HFOV and iNO therapy is often more successful than treatment with HFOV or iNO alone in patients with PPHN, especially in patients with respiratory distress syndrome or MAS as the underlying disease\(^ {31}\).

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. However, a double-blind trial of hydrocortisone use did not show a beneficial effect\(^ {41}\). 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 well studied.

Phosphodiesterase (PDES) inhibitor-Sildenafil, Milrinone

Sildenafil inhibits cGMP specific PDES type 5 (PDE-5), increases cGMP concentration, and may result in pulmonary vasodilatation or enhance the activity of NO. Because PDE-5 is primarily distributed within the smooth muscle of the arterial wall in the lungs and penis, sildenafil acts selectively in both areas without inducing vasodilation in other areas of the body. Sildenafil is only available in enteral form in the market. Baquero et al. reported that oral sildenafil improved OI in infants with severe PPHN\(^ {35}\). The dose is 0.3–1 mg/kg/dose via an orogastric tube every 6–12 hours. The potential side effects include worsening of oxygenation, systemic hypotension, and bleeding.

Milrinone is a specific PDE-3 inhibitor, which increases the cAMP concentration and decreases pulmonary vascular resistance.

Potential therapy for PPHN in MAS

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).

Extracorporeal membrane oxygenation (ECMO)

The use of adjunctive therapies has dramatically decreased the need for ECMO therapy in the last decade\(^ {36}\), but some infants with MAS and PPHN still develop severe hypoxic respiratory failure despite the optimal medical treatments\(^ {27}\). ECMO provides cardiopulmonary support while allowing the underlying pulmonary or cardiac dysfunction to resolve without the risk of further injury from barotrauma or hyperoxia. The ECMO treatment results in a 94% survival rate in these high risk infants who had a predictive mortality rate of 80% without ECMO therapy.
The selection criteria include:
1) Gestation age of at least 34 weeks.
2) Birthweight of at least 2,000 g.
3) Lack of major coagulopathy or active bleeding.
4) No major intracranial bleeding.
5) Mechanical ventilation of less than 10-14 days duration and reversible lung disease.
6) Failure of optimal medical management and infants who have a high predicted mortality rate.

Oxygen index (OI) and alveolar-arterial difference in oxygen tension (A-aDO$_2$) are commonly used to predict the likelihood of mortality. The OI of 40 or greater and/or A-aDO$_2$ greater than 600 mmHg are predictive of an 80% risk of mortality.

**OUTCOME OF MECONIUM ASPIRATION SYNDROME**

The mortality rate of MAS-related illness has declined over the decades: 4.2% during 1973–1987 in the USA to 2.5% during 1995–2002 in Australia and New Zealand. The perinatal deaths are related to perinatal depression, airway obstruction, and development of PPHN.

Pulmonary sequelae are common in infants with severe MAS. Nearly 50% of the infants had episodes of reactive airway disease during the first 6 months of age. Mild airway obstruction or exercise-induced asthma were more common in these children at 6–8 years.

Long-term neurological outcomes of infants with MAS depend upon the underlying disorders. The neurological outcomes are related to the presence or absence of intrauterine asphyxia, hypoxic-ischemic encephalopathy, and PPHN. Infants who required ECMO treatment had more complications than those who did not.

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