REVIEW ARTICLE

Meconium aspiration syndrome: a comprehensive review

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Meconium aspiration syndrome (MAS) is a complex respiratory disease that continues to be associated with significant morbidities and mortality. The pathophysiological mechanisms of MAS include airway obstruction, local and systemic inflammation, surfactant inactivation and persistent pulmonary hypertension of the newborn (PPHN). Supplemental oxygen and non-invasive respiratory support are the main therapies for many patients. The management of the patients requiring invasive mechanical ventilation could be challenging because of the combination of atelectasis and air trapping. While studies have explored various ventilatory modalities, evidence to date does not clearly support any singular modality as superior. Patient's pathophysiology, symptom severity, and clinician/unit expertise should guide the respiratory management. Early identification and concomitant management of PPHN is critically important as it contributes significantly to mortality and morbidities.

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INTRODUCTION

Meconium aspiration syndrome (MAS) describes a neonatal respiratory illness secondary to aspirated meconium-stained amniotic fluid (MSAF), which is characterized by hypoxemia and respiratory distress. Meconium is the first stool of an infant, and is composed of cellular debris, amniotic fluid, vernix, lanugo, bile, pancreatic enzymes, and other substances of the digestive tract [1]. Fetal distress or intrauterine hypoxia may trigger prenatal passage of meconium into the amniotic fluid. Aspiration of MSAF can lead to airway obstruction, pulmonary inflammation, and surfactant inactivation. Some neonates present with only mild tachypnea, but others can experience severe respiratory failure. As meconium is rarely present in the lower intestinal tract prior to 34 weeks gestation, MAS is typically a disorder of full term (≥37–40 weeks gestation), near-term, and post-term infants [2].

Historical estimates of MSAF incidence range from 7–22%, with MAS incidence between 0.5–2 per 1000 live births [3, 4]. Advanced gestation has been associated with increased risk for MAS [5, 6]. A recent study from 2022 demonstrated an increase in MAS from 1.3% at 38 weeks to 4.8% at 41 weeks [5]. Thick meconium, non-reassuring fetal heart tones and subsequent Apgar score <7 at one minute all confer increased risk for MAS [6, 7]. There also appears to be an association between MAS and the method of delivery, with the highest rates of MAS occurring in infants who underwent emergency cesarean section [8, 9]. Planned home birth has also been associated with an increased risk of MAS, although these results are not uniform across studies [10]. Additionally, some studies have suggested a link between increased incidence of MAS and certain maternal races/ethnicities, including Black American or African, Pacific Islander, and indigenous Australian [8, 9, 11].

A study of 132,884 term newborns in France found the incidence of MSAF to be 7.9% and the overall incidence of MAS to be 0.2%, while a study of 2,490,862 neonates in Australia and New Zealand revealed rates of MAS as low as 0.35 per 1000 live births [12, 13]. The incidence of MAS is reported to have decreased over recent decades [14]. This overall decrease in the incidence of MAS is likely a result of improved prenatal care and surveillance in many countries around the world, as well as changes in obstetric practice resulting in fewer post-term deliveries with earlier induction dates and possibly more rapid response to non-reassuring fetal well-being during the labor process [11, 14].

Management of patients with MAS is frequently challenging. Infants may require significant cardiopulmonary support in the neonatal intensive care unit (NICU). MAS is associated with a significant risk of mortality and morbidities including persistent pulmonary hypertension of the newborn (PPHN), air leaks, and hypoxic-ischemic encephalopathy (HIE).

PATHOPHYSIOLOGY

Meconium affects the respiratory system through multiple pathophysiological mechanisms. We broadly categorize contributing mechanisms below and in Fig. 1.

Local inflammation in the lungs

Animal studies on the effect of meconium in the lung showed indicators of significant local inflammation. Bronchoalveolar lavage following meconium aspiration showed a significant increase in alveolar neutrophil counts and neutrophil chemotactic activity up to 48 h after aspiration, in addition to significant influx of plasma protein [15]. Additionally, there is an increase in inflammatory mediators including cytokines, interleukins, reactive oxygen species and complement activation in the lungs [1]. This inflammation promotes the death of airway and alveolar epithelial cells in the setting of meconium aspiration [16].

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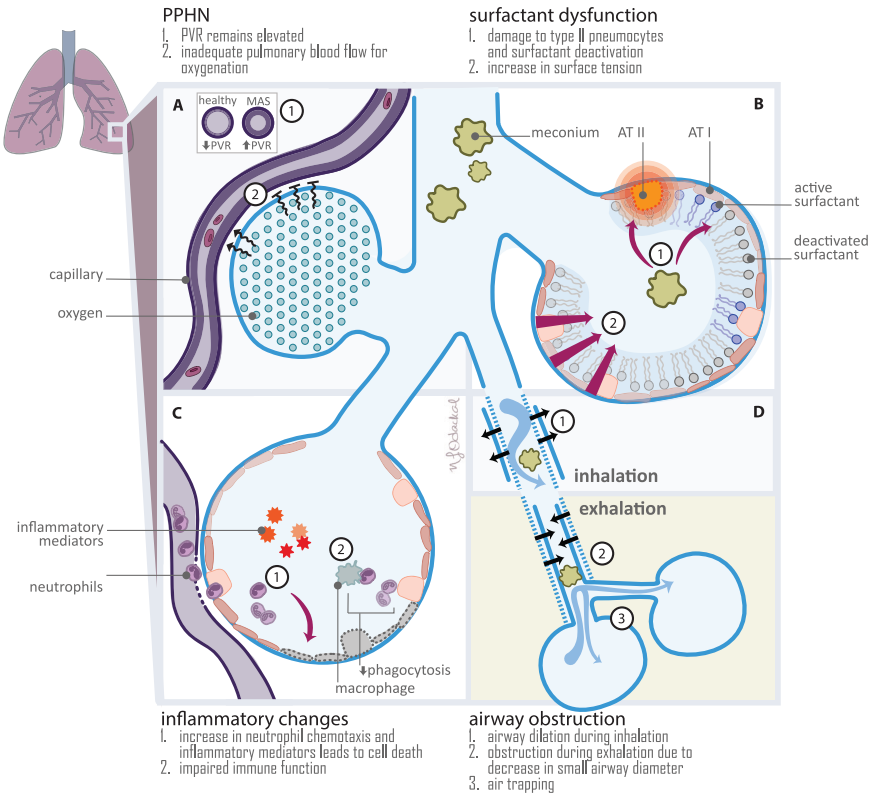

Fig. 1 Pathophysiology of Meconium Aspiration Syndrome.

Local effects/mechanical airway obstruction

Large particles of aspirated meconium can block large airways, leading to severe hypoxia. The obstruction of smaller airways is more common and may lead to a ball-valve like effect. The increase in small airway diameter during inspiration makes this obstruction partial and allows for inflation of the alveoli distally. However, the decrease in small airway diameter during expiration leads to complete obstruction and prevents deflation of the alveoli. With recurrent breaths, this overdistension may result in pneumothorax and other air leak syndromes. Obstruction of small airways may also lead to alveolar collapse and ventilation-perfusion mismatch. MAS is associated with increased functional residual capacity (FRC) and radiographic evidence of lung hyperinflation [17]. Further, there is evidence of microvascular endothelial damage and fluid accumulation [18].

Surfactant inactivation

Meconium directly damages the surfactant producing type II pneumocytes. The inflammatory response in the alveoli and the components of meconium, including bilirubin and bile salts, change the chemical properties of surfactant and render it inactive [19, 20]. In experimental studies, the surface tension of alveoli increased progressively with the amount of aspirated meconium [20]. In clinical studies, MAS is associated with decreased dynamic and static lung compliance [17], depicted by the pressure-volume loop in Fig. 2.

Systemic inflammatory response and negative effect on the immune system

Meconium in the gastrointestinal tract is considered "extracorporeal," and the immune system does not identify it as "self." While MAS is largely thought of as a respiratory condition, a systemic inflammatory response likely contributes to the pathophysiology in addition to local lung inflammation. The changes in systemic markers of inflammation in neonates with MAS correlates with the

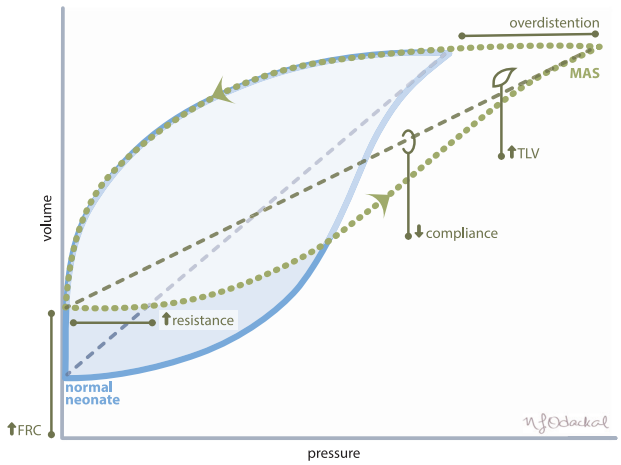

Fig. 2 The Pressure-Volume Curve of the lungs in Neonates with Meconium Aspiration Syndrome Compared to that of Healthy Neonates.

severity of lung disease. Hofer et al reported on neonates with MAS without early onset sepsis and found these neonates to have significantly lower white blood cell counts (WBC) and absolute neutrophil counts (ANC), and elevated C-reactive protein (CRP) and immature-to-total neutrophil ratios (I:T-ratio) [21]. A systemic inflammatory effect mediated through the complement system may also play a role in the pathophysiology of MAS [22]. Alveolar macrophages have reduced phagocytic and respiratory burst activities in the setting of meconium aspiration, while neutrophils have similarly reduced phagocytic activity. In-vitro studies have suggested a role for pancreatic enzymes in the pathogenesis of MAS based on the protective effect of protease inhibitors on epithelial cells [23].

Persistent pulmonary hypertension of the newborn (PPHN)

One of the most significant sequelae of MAS is PPHN, which results from impaired fetal to perinatal physiologic transition. Conversely, in term newborns, MAS represents one of the most significant risk factors for PPHN [24]. In MAS, sick lungs and hypoxia contribute to PPHN. Here, pulmonary vascular resistance (PVR), which is elevated throughout fetal development, fails to decrease sufficiently after birth to permit adequate pulmonary blood flow required to achieve oxygenation through newly inflated neonatal lungs. Inadequate oxygenation results in further hypoxemia, which may vary from mild to critical across the spectrum of disease severity. Important to consider in its therapeutics, MAS-PPHN is typically associated with normal fetal pulmonary and cardiovascular development, such that elevated PVR occurs in the context of a reactive pulmonary vascular bed with "sick" lungs causing pulmonary vasoconstriction rather than underlying pulmonary vascular maldevelopment more associated with "fixed" elevations in PVR [25, 26].

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical features

The presence of MSAF is a prerequisite for MAS. Aspiration of this MSAF perinatally triggers the pathophysiologic cascade that results in MAS [27, 28]. Clinically, neonates with MSAF may range from asymptomatic to symptomatic; neonates with true MAS demonstrate respiratory symptoms shortly following delivery, including tachypnea, cyanosis, grunting, and increased work of breathing. Additionally, a hyperexpanded thorax or "barrel-shaped chest" may be apparent, and evidence of meconium-staining may be present on the skin, hair, nails, and umbilical cord. Rales and rhonchi may be heard on auscultation. Across the spectrum of disease severity, neonates with MAS may range from vigorous with only mild tachypnea and minimally decreased oxygen saturations to severely depressed with HIE and hypoxic respiratory failure [29, 30].

Classically, chest radiograph in MAS demonstrates pulmonary hyperinflation with patchy infiltrates alternating with areas of atelectasis; however, radiological findings may be variable and disease severity by imaging does not correlate with clinical disease severity [27, 31]. Arterial blood gas may show low PaO_2 levels consistent with hypoxemia. Respiratory alkalosis may be present initially due to tachypnea and hyperventilation, but respiratory acidosis may also be seen with hypercarbia. With increasing disease severity, hypoxia- often coupled with metabolic acidosis- can affect the cardiovascular status and impair tissue oxygen delivery, further driving PPHN, cardiac dysfunction, and potential for end-organ injury.

The hallmark of PPHN is hypoxemia with differential saturations: elevated pulmonary vascular pressures result in right-to-left shunting across the ductus arteriosus, producing a gradient observed between higher pre-ductal saturations and lower post-ductal saturations [25, 26]. With severe or advanced disease, sequelae of right heart and eventual left heart failure are observed, including hypotension and lactic acidosis [26]. Clinically, neonates with PPHN may be highly labile with respect to saturations and other vital sign parameters, with poor tolerance for lights, sounds, and other stimuli.

Diagnosis

The differential diagnosis for MAS includes transient tachypnea of the newborn, sepsis, cyanotic congenital heart disease, as well as neonatal respiratory illnesses such as pneumonia, respiratory distress syndrome (RDS), pneumothorax and other air leak syndromes, developmental lung abnormalities including congenital airway and lung abnormalities (such as congenital pulmonary adenomatous malformation), thoracic or pulmonary masses, and alveolar capillary dysplasia, among others. Most often, a clinical history of MSAF combined with postnatal hypoxemia and characteristic chest radiographic findings help differentiate MAS from other neonatal cardiac and respiratory conditions. The following diagnosis of MAS has been utilized in clinical trials [32]:

- Respiratory distress in a neonate born through MSAF.
- Supplemental oxygen required to maintain oxygen saturations.
- Oxygen requirement beginning in the first two hours of life and lasting for 12 h or longer.
- Absence of congenital malformations of the airway, lung, or heart.

PPHN can be diagnosed clinically by the presence of differential saturations, with ≥10 percentage point difference between higher pre-ductal and lower post-ductal saturations, reflecting shunting of deoxygenated blood from the pulmonary artery into the aorta. Formal diagnosis relies on echocardiography, which is also important to rule out accompanying congenital heart disease, which may complicate cardiopulmonary management or contribute to cyanosis, and to guide optimal choice of therapeutics [25, 26, 33]. While consensus definition in neonatal populations are problematic, echocardiographic findings supporting PPHN include elevated pulmonary artery pressure measurement, leftward deviation of the interventricular septum, tricuspid regurgitation, bidirectional and/or right-to-left flow across fetal shunts (ductus arteriosus, patent foramen ovale), as well as right ventricular hypertrophy, dilation, or dysfunction [25].

MAS and PPHN disease severity can be assessed using the oxygenation index (OI), ideally calculated from a pre-ductal arterial sample: $OI = (\text{mean airway pressure} \times FiO_2 \times 100) / PaO_2$, where FiO_2 equals fraction of inspired oxygen. Generally, OI values ≤ 15 reflect mild respiratory disease, while levels ≥25 reflect severe hypoxic respiratory failure [25, 28]. Alternatively, OI can be estimated using the pre-ductal oxygen saturation to calculate an Oxygen Saturation Index (OSI), where OSI × 2 approximates the OI value. $OSI = (\text{mean airway pressure} \times FiO_2 \times 100) / \text{pre-ductal oxygen saturation}$ [34].

CLINICAL MANAGEMENT

Optimal management of MAS begins in the prenatal period and extends well beyond delivery. We present updated evidence and expert consensus to describe perinatal management, oxygen and respiratory support approaches, surfactant therapy, PPHN management, and other factors to consider in the care of neonates with MAS (Table 1).

Perinatal and delivery room (DR) management

Recommendations for the perinatal management of neonates born through MSAF have evolved dramatically over the past few decades. Based largely on limited data from the 1970s, obstetric practice up to 2005 consisted of suctioning the nasopharynx and oropharynx after the delivery of the fetal head, but before the delivery of the shoulders and body [35]. Since 2005, this is no longer recommended because it was found to be associated with increased DR morbidity and/or need for DR resuscitation, as well as ineffective in preventing or altering the course of MAS [32, 36]. Amnioinfusion has also been trialed to decrease the risk of MAS, with the goal of diluting the meconium and relieving cord compression if oligohydramnios is also present [37]. However, a large RCT in 2005 found no reduction in the incidence of MAS or perinatal mortality with this practice [38]. A Cochrane review again supported this conclusion in 2010 [39]. Since 2006, the American Academy of Obstetricians and Gynecologists (ACOG) no longer recommends routine amnioinfusion for the reduction of MAS [40].

Table 1. Summary of Clinical Presentation and Management of Infants with Meconium Aspiration Syndrome.

Clinical History	Clinical Presentation	DR	Respiratory	PPHN	Other Considerations
Post-dates delivery	Perinatal time	Focus on initiating resuscitation (position airway, suction mouth, and nose, dry, and stimulate)	Oxygen supplementation • Nasal cannula • Oxyhood	Cardiovascular support • Dobutamine • Epinephrine • Vasopressin • Milrinone	Antibiotics
Meconium-stained amniotic fluid	Hypoxemia	Do not delay PPV for infants without respiratory effort	CPAP to support lung recruitment	Prostaglandin (PGE1)	Sedation
Category II/III fetal heart tracing	Tachypnea, respiratory distress/ increased work of breathing	Routine intubation of non-vigorous infants not indicated	Mechanical ventilation • Conventional • High frequency	Hydrocortisone	Minimize environmental and other stimuli
Sentinel perinatal event	Barrel-chested appearance	Consider intubation/ tracheal suctioning in non-vigorous infants with meconium preventing effective PPV	Surfactant	Pulmonary vasodilator therapies • Oxygen • iNO • Sildenafil • Prostacyclin	
	CXR: hyperinflation, patchy opacities, and atelectasis	Post-resuscitation care and monitoring	PaO_2 Target: 60–80 mmHg. $PaCO_2$ Target: 45–60 mmHg	pH Target: 7.25–7.4	
			ECMO		

- From a neonatal standpoint, resuscitation recommendations for infants born through MSAF have evolved significantly. In the 1990s there was a shift of practice from routinely intubating and suctioning the airway of all infants born through thick MSAF to only intubating and suctioning non-vigorous infants. The shift occurred following evidence that routine intubation and suctioning of vigorous infants with MSAF did not decrease the incidence of MAS and could potentially cause laryngopulmonary complications [41, 42]. The 2000 Neonatal Resuscitation Program (NRP) guidelines reflected this practice change [36, 43].

Routine tracheal intubation and suctioning of all non-vigorous infants with MSAF remained the standard of care until 2015. An RCT from India demonstrated that routine endotracheal suctioning in non-vigorous neonates with MSAF did not significantly reduce the risk of MAS or its associated morbidity [44]. Due to insufficient evidence, the 2015 American Heart Association guidelines no longer recommended this practice [45], and this change was reflected in the NRP 7th Edition [46]. The focus was placed on initiating steps of resuscitation (positioning the airway, suctioning the mouth and the nose, drying, stimulating) and not delaying delivery of positive pressure ventilation (PPV) to infants without respiratory effort; endotracheal intubation could still be appropriate in non-vigorous infants for whom meconium was obstructing the airway and preventing effective PPV [45]. A retrospective study of DR management noted that recovery of meconium below the cords was observed in 47% of infants who developed MAS, supporting the theory that aspiration of meconium often takes place in-utero [7]. Although the evidence is of low certainty, these 2015 recommendations have remained in place for the NRP 8th edition [47] as the majority of evidence continues to suggest that routine endotracheal suctioning of non-vigorous neonates does not decrease the incidence of MAS [48–56].

Respiratory management

Respiratory support for MAS ranges from the delivery of oxygen therapy (nasal cannula, oxyhood, high flow nasal cannula) to continuous positive airway pressure (CPAP) to mechanical ventilation in more severe cases. First, considerations for assessment and monitoring in patients with MAS beyond the DR, which should be individualized to disease severity.

Monitoring and therapeutic targets

Both pre- and post-ductal saturation monitoring should be performed in the presence of an open ductus arteriosus to enable minute-to-minute monitoring of ductal shunting, which will reflect relative pulmonary to systemic pressure differentials. Because PPHN results in right-to-left ductal shunting, pre-ductal saturations should be used to adjust therapies and oxygen supplementation. Key indices for serial monitoring include pre-ductal saturations, PaO_2 values, and OI.

Universally, consensus guidelines support target preductal oxygen saturation goals with aggressive avoidance of hyperoxemia and hypoxemia [57]. Across literature, a target saturation range with lower limit of 91–92% and upper limit of 95–97% appears consistent [31, 57–59]. Because oxygen is a potent pulmonary vasodilator, avoidance of extremes in either direction will support clinical stability and minimize injury. Animal models suggest a clinically important inflection point in hypoxic pulmonary vasoconstriction at preductal PaO_2 values around 60 mmHg, such that contemporary recommendations suggest targeting a preductal PaO_2 of at least 60–80 mmHg [26, 60–62]. Further, animal and neonatal studies demonstrate that while supplemental oxygen accelerates the rate of PVR decrease after birth, persistent hyperoxia contributes to inflammation, developmental lung injury, oxidative stress, and diminishes subsequent nitric oxide responsiveness [59, 60, 63–65].

Assessment and monitoring of moderate-to severe MAS and associated PPHN may be best achieved with continuous hemodynamic monitoring and frequent blood gas/lactate laboratory evaluation during the acute phase. For sicker patients, arterial access via right radial arterial line should be prioritized over umbilical arterial catheterization to permit pre-ductal assessments and OI calculations. Serial arterial blood gas measurements can be particularly important in caring for MAS-PPHN, as expert-consensus provides guidelines to target for pH, PaO_2, $PaCO_2$. Serum lactate may be useful as an objective marker of tissue perfusion. Increasingly, b-type natriuretic peptide (BNP, NT-pro BNP), is being recognized as an important clinical biomarker in PPHN representing right heart strain, with utility in trending disease status and response to therapies [57].

In the setting of full term and near-term neonates with normal fetal lung development, "normo-ventilation" is recommended with a target $PaCO_2$ level of 45–60 mmHg [57].

Oxygen therapy

In mild MAS, supplemental oxygen, most commonly in the form of a nasal cannula or oxyhood, is often all that is required [27, 31]. The goal of supplemental oxygen is to provide adequate oxygenation, which is one of several essential factors in helping to prevent or minimize the effects of PPHN [28, 31]. Historically, supplemental oxygen alone (nasal cannula or oxyhood) had often been the preferred treatment of mild MAS, in an attempt to limit risk of air trapping and resultant air leak [66, 67].

Continuous positive airway pressure (CPAP)

Current recommendations favor the least invasive form of respiratory support in the management of MAS, while still ensuring adequate oxygenation and ventilation [68]. The use of CPAP in MAS has been proposed as a way of preventing intubation and mechanical ventilation by optimizing lung recruitment (setting PEEP at 6–8 cmH_2O) and limiting oxygen exposure [27], and about 10–20% of infants are treated with CPAP alone [31]. The respiratory management of these infants is complex due to the presence of both atelectasis and hyperinflation, and the degree of pressure required will be unique for each patient [27]. Although there is an increased risk of air leak, known benefits of CPAP include improvement in atelectasis, reduced air trapping, and decreased ventilation-perfusion mismatch, ultimately improving gas exchange [67]. A 2018 RCT demonstrated a reduced need for mechanical ventilation in the first 7 days of life utilizing low level CPAP (5 cmH_2O) versus oxyhood support [69]. This study concluded that early use of CPAP compared to oxyhood resulted in one newborn avoiding mechanical ventilation for every five newborns with MAS [69].

Intubation and mechanical ventilation

In current practice, about one-third of patients with MAS require endotracheal intubation and mechanical ventilation. Earlier studies reported higher rates of intubation, with Hofer et al. reporting invasive mechanical ventilation rates of 76% for infants with MAS from 1990 to 2010 [30], while more recent population-based studies report intubation and mechanical ventilation in 35% of MAS patients [13].

In our practice, endotracheal intubation is generally indicated when the FiO_2 reaches 60%, for hypercapnia with $PaCO_2 \geq 60$, or for pH < 7.25. Hemodynamic instability with low blood pressure and poor systemic perfusion is another indication for mechanical ventilation. When non-emergent, we preferably perform endotracheal intubation with premedication for sedation. Appropriate size endotracheal tube should be selected, which is usually a size 3.5 - 4 mm (internal diameter) tube for most term neonates.

In animal models, partial liquid ventilation with surfactant administration resulted in improved surfactant distribution and oxygenation [70]. However, no studies to date have evaluated liquid ventilation in humans. In current practice, the mode of ventilation depends primarily on clinician and unit-level factors. While large, prospective RCTs comparing modes of ventilation for infants with MAS do not exist, observational studies and smaller trials have shown improved short-term outcomes with high frequency ventilation (HFV), including shorter duration of intubation, greater improvement in PaO_2, and reduced incidence of air leak [71, 72].

Conventional mechanical ventilation (CMV)

CMV is the most widely used ventilatory mode for infants with MAS. Specific settings are largely based on clinical experience and physiological reasoning. A recently published study found that infants with MAS require higher tidal volume (V_T, mean ± SD of 6.11 ± 1.05 mL/kg) and minute ventilation (371 ± 110 mL/kg/min) compared to V_T of 4.86 ± 0.77 mL/kg and minute ventilation of 262 ± 53 mL/kg/min for infants without MAS [73]. The following provides details for specific ventilator parameters.

Settings for positive end expiratory pressure (PEEP). Choosing the PEEP level should balance maintaining FRC with adequate pressure against the potential risk of reduced oxygenation and pneumothorax with hyperinflated lungs. In an earlier study, Fox et al. reviewed the response of 14 patients with MAS to various levels of PEEP; some of these patients were breathing spontaneously and received nasal CPAP, while others received mechanical ventilation via endotracheal tube. This Historical study has suggested an optimal PaO_2 response demonstrated at PEEP of 4–7 cmH_2O for MAS [74]; clinically, a PEEP of 5–8 cmH_2O is generally used depending on observed atelectasis and hyperinflation.

Settings for inspiratory time (iT) and rate. The time constant is the time required for the pressure to equilibrate between the alveoli and the proximal airway. It takes three time constants to discharge 95% of the tidal volume on expiration [75]. The time constant varies with both airway resistance (R_{aw}) and lung compliance (C_L) [75], with time constant (K_t) = C_L X R_{aw}. The inspiratory K_t is shorter than the expiratory K_t because airway resistance is lower during inspiration due to airway dilation. With insufficient time for expiration, incomplete emptying of the lungs may result in increased pressure within the airways and alveoli, leading to "auto PEEP." This increases the risk of pneumothorax and negatively affects oxygenation [75]. The optimal ventilatory rate and iT should minimize the risk of incomplete expiration and the development of "auto-PEEP." Generally, ventilatory rate is set at 30 to 40 breaths per minute or less, with iT usually between 0.35–0.4 s. However, iT as high as 0.5 s has been reported [31].

Settings for peak inspiratory pressure (PIP). PIP should be sufficient to help open the areas of the lung with atelectasis and reduced compliance. Depending on the degree of parenchymal disease, increased PIP may be required. When PIP requirements approach 30 cmH_2O, high frequency ventilation should be considered to minimize lung injury, overdistension, and air leak [31]. Alternatively, volume ventilation has been suggested by several groups, with a mildly increased proposed target V_T around 6 mL/kg [31, 73].

High frequency ventilation (HFV)

HFV may help protect the lungs from both alveolar overdistension (volutrauma) and alveolar collapse (atelectotrauma) [76]. Despite limited population-specific clinical studies, HFV has become an important tool in the management of infants with MAS. About one quarter of infants with MAS requiring mechanical ventilation are treated with HFV, with reported use increasing over time [42, 77, 78]. High Frequency Oscillatory Ventilation (HFOV) is the most frequently used mode of HFV, followed by High Frequency

Jet Ventilation (HFJV). HFV may be used as a primary ventilatory approach or as a rescue mode following CMV. Transitioning to HFOV usually occurs in the setting of persistent hypercapnia, air leak, or when combined with nitric oxide (iNO) in the setting of PPHN [79]. Importantly, Kinsella and colleagues demonstrated that lung recruitment with HFOV augmented iNO responsiveness in MAS [79]. A stepwise recruitment maneuver using oxygenation as an indirect indicator of lung inflation helps in identifying the ideal mean airway pressure (Paw) to optimize lung volume. In our unit, these infants usually require Paw of 16 to 22 cmH_2O for optimal oxygenation. HFOV frequency is usually set at 8–10 Hz. Considering HFJV, preclinical studies have shown beneficial effect in MAS [80–82], and Dargaville reported on infants with MAS improving on HFJV after transitioning from HFOV using a low frequency (240–360 bpm) combined with low CMV rate [31].

Heliox

Heliox has been clinically used in the management of many pediatric respiratory diseases including asthma and bronchiolitis. Heliox is a gas composed of a higher percentage of helium (usually 70–80%) and a lower percentage of oxygen (usually 20 to 30%) [83]. Helium is a naturally occurring gas with low density, whose physical properties support laminar flow even with small diameter airways prone to turbulent flow. A recent RCT compared outcomes of mechanically ventilated infants with MAS who received Heliox for six hours followed by blended oxygen and air against those receiving blended oxygen and air [84]. In this study, infants with MAS treated with Heliox had significantly better oxygenation as measured by PaO_2/FiO_2, shorter time on mechanical ventilation, and decreased hospital length of stay. Although this study and others have established feasibility of Heliox in infants with MAS requiring mechanical ventilation, more studies are needed to operationalize its use clinically in this population [85, 86].

Surfactant therapy

MAS-associated surfactant inactivation can be treated with exogenous surfactant, which has been shown to improve oxygenation and lung compliance in animal models [87]. There are two main ways surfactant can be administered: through a bolus dose (as is used to deliver surfactant to infants with RDS) or via surfactant lung lavage. Bolus surfactant has become an adjunct treatment for many infants with MAS, and a 2014 Cochrane review concluded that bolus surfactant administration may reduce the severity of respiratory illness and decrease the need for extracorporeal membrane oxygenation (ECMO) [88, 89]. Further, reduction in the need for ECMO with bolus surfactant was one conclusion in a 2016 systematic review [90].

Several RCTs and systematic reviews have looked at the use of lung lavage with dilute surfactant. The goal of surfactant lung lavage is not only to replace surfactant, but also to remove meconium and debris from the lung, thereby improving lung function [87]. Although the evidence is inconsistent, the use of surfactant lavage for MAS appears to be safe [91]. A 2012 systematic review and meta-analysis found surfactant lavage therapy to decrease death or need for ECMO [92]. However, this conclusion was of low-quality evidence because of a total sample size less than 100 in the two RCTs included in these studies [89, 92]. Two additional RCTs concluded that while surfactant lung lavage was well tolerated, it did not alter the duration of respiratory support [93, 94]. Similarly, a 2020 meta-analysis concluded that surfactant lavage improved OI and reduced duration of mechanical ventilation but did not shorten the duration of oxygen therapy or hospital stay [91].

While surfactant appears beneficial in MAS, the superior route of administration is less clear. A 2016 review comparing bolus to surfactant lavage found both routes to reduce the duration of mechanical ventilation and hospital stay [90]. Subsequently, a 2019 RCT concluded no additional benefit to surfactant lavage over bolus surfactant in MAS [95].

PPHN management

In patients with MAS, PPHN is associated with significant morbidity and mortality, such that timely diagnosis and optimal management is critical. For MAS-PPHN, management is similar to that for PPHN across neonatal populations: support pulmonary blood flow and systemic oxygen delivery through support of cardiac function and systemic blood pressure as well as targeted pulmonary vasodilator therapies. However, we endeavor to highlight when research has identified strategies unique to MAS-PPHN. As a general rule, core management aims include cardiopulmonary optimization, adequate tissue oxygen delivery, and avoidance of iatrogenic injury [58]. Given that pulmonary disease represents a key underlying pathophysiologic mechanism responsible for hypoxemia and pulmonary vasoconstriction, lung recruitment and pulmonary optimization remain the key initial interventions for MAS-PPHN [33].

Cardiovascular management

Pumping against elevated pulmonary pressures causes right heart strain, resulting in potential for right heart dysfunction and failure. Compounded by the effects of hypoxia, acidosis, and other factors, unsupported right-sided heart failure leads to decreased left heart filling, left-sided dysfunction and diminished cardiac output, with ultimate risk for systemic shock [26]. Therefore, the choice of inotropic agent should be patient-specific to disease state and pathophysiology, with careful consideration of therapeutic goals. While dopamine remains the most widely studied cardiovascular agent in neonates, studies suggest the risk-benefit profile of other agents may be superior in the treatment of PPHN; dopamine's non-selective systemic and pulmonary vasoconstriction make it particularly problematic in the PPHN population, for whom a major therapeutic goal is reduction of PVR [96]. Rather, expert consensus supports the choice of dobutamine and/or epinephrine to support cardiac function in PPHN. Dobutamine acts as a pure inotrope without vasoconstrictor properties, making it an excellent choice to support right heart function in the setting of adequate systemic blood pressure, without concomitant increases in PVR [97]. When cardiac dysfunction is compounded by hypotension, epinephrine is typically the agent of choice for its combined inotropy and vasoconstriction, with early data suggesting less effect on pulmonary vasoconstriction compared to dopamine [98]. In PPHN patients with preserved cardiac function but with inadequate systemic blood pressure, vasopressin is increasingly utilized as a systemic vasoconstrictor with reported improvements in both oxygenation and systemic perfusion [96, 99]. At current, studies are exploring norepinephrine and other cardiovascular agents, however data remains lacking to clearly support their use in the PPHN population. While historically relegated to cardiac and cardiac surgical populations, milrinone is now widely utilized in PPHN, particularly in the setting of right or left heart dysfunction once appropriate blood pressure has been established [33]. Milrinone, a phosphodiesterase (PDE) III inhibitor, improves cardiac inotropy and lusitropy, with the additional benefit of pulmonary vasodilation through its effects on the prostacyclin-cAMP pathway. Milrinone may additionally provide synergistic pulmonary vasodilation when combined with other pulmonary hypertension agents [100–103]. However, milrinone may also decrease systemic blood pressure through non-selective vasodilation and relies on renally-mediated clearance, requiring caution and thoughtful consideration for appropriate therapeutic candidates [96]. While few head-to-head vasodilator trials exist for the PPHN population, one recent RCT comparing milrinone to sildenafil reported superior oxygenation among milrinone-treated patients and no significant hypotension among either group [104].

Prostaglandin E1 (PGE1) has a long clinical history in neonatal ductal-dependent critical congenital heart disease, utilized to maintain patency of the ductus arteriosus for support of pulmonary or systemic perfusion as a bridge to cardiac surgical intervention. More recently, PGE1 has been considered as "rescue therapy" in severe PPHN to preserve ductal patency with the goal of offloading a failing right ventricle. One small retrospective study suggested benefit in PPHN when neonates with hypoxic respiratory failure, but not ductal-dependent congenital heart disease, were administered PGE1 [105]. While no studies have specifically explored PGE1 use in MAS-PPHN, its use is increasingly supported in diverse PPHN populations associated with supra-systemic pulmonary artery pressures and/or right ventricular failure [57, 106–108].

Glucocorticoids represent another potentially important therapeutic agent, particularly in MAS-PPHN owing to their anti-inflammatory effects [109, 110]. While early studies proved inconclusive [111], more recent studies exploring mechanisms of action suggest clinical benefit: animal and clinical studies suggest hydrocortisone improves oxygenation and may attenuate oxidative stress [106, 112, 113]. As an added benefit, one study additionally reported improved systolic blood pressure among neonates with PPHN following hydrocortisone administration [106].

Pulmonary vasodilator therapies

Within the lungs, three major biochemical pathways drive PVR: nitric oxide pathway (NO-cGMP), prostacyclin pathway (PGI_2-cAMP), and endothelin pathway [114]. All currently available pharmacotherapy targets for pulmonary hypertension act on one of these three vasoreactive pathways. The first vasodilator therapy utilized in the management of MAS is oxygen, itself a potent pulmonary vasodilator. However, judicious oxygen supplementation to achieve target preductal saturations while avoiding hyperoxia is critical to support clinical stability and minimize lung injury.

Inhaled nitric oxide (iNO) targets the NO-cGMP pathway and is the only FDA-approved agent for PPHN, with demonstrated reduction in need for ECMO [115]. Therefore, once lung optimization is achieved, iNO is the first-line pulmonary vasodilator therapy for term and near-term infants with OI ≥ 25 [33, 57, 116]. Specific to MAS-PPHN, one study reported decreased duration of ventilation and oxygen support following treatment with iNO [117]. Particularly among patients with MAS-PPHN, improved oxygenation in response to iNO therapy is amplified with the synergistic effect of HFOV [79, 118].

However, significant iNO nonresponders/transient responders have limited its utility as the panacea for PPHN [115]. Further, limited historic data suggests less significant and/or unsustained iNO responses in the setting of MAS compared to idiopathic PPHN, surmised to be the result of underlying ventilation-perfusion mismatch and airway obstruction characteristic of MAS [119, 120].

Sildenafil, a PDE5 inhibitor, also exerts its effects through the NO-cGMP pathway. While FDA warnings around the use of sildenafil in children must be considered [121], both US and European expert consensus guideline statements support consideration for sildenafil in PPHN, in either oral or intravenous preparation and as monotherapy or adjunct therapy, especially when iNO is unavailable or fails to sufficiently improve oxygenation [33, 57].

Prostacyclin analogs represent the class of pulmonary vasodilator medications targeting the PGI_2-cAMP pathway. Formulations exist as inhaled, intravenous, and subcutaneous infusions. While less studied in pediatric and neonatal populations than iNO or sildenafil, early studies appear promising, and current guidelines support consideration for the use of prostacyclin analogues as an adjunct therapy in PPHN [33].

Normalization of acid-base status

Since acidosis exaggerates hypoxic pulmonary vasoconstriction [61], correcting severe metabolic acidosis to target a pH 7.25–7.4 during acute stabilization is recommended [57]. Figure 1.

Extracorporeal membrane oxygenation (ECMO)

ECMO has a well-established history in the treatment of severe MAS-PPHN. Historically, the first neonate successfully treated with ECMO in 1975 was a one-day old with MAS [122]. While MAS once comprised a majority percentage of the neonatal conditions for which ECMO was utilized [106], decreased frequency of MAS over recent decades has translated into decreased ECMO use for MAS-PPHN [122–124]. Importantly, survival rates following ECMO for MAS-PPHN remain excellent, with recent data suggesting survival beyond 90%, likely reflecting the "reversible" nature of this cardiopulmonary disease [122, 125].

Today, ECMO is indicated to improve survival in severe MAS-PPHN with inadequate or unsustained response to cardiopulmonary medical optimization [33, 126]. Extracorporeal Life Support Organization (ELSO) guidelines support the following criteria for ECMO initiation in neonates with severe cardiorespiratory failure: inadequate tissue oxygen delivery on maximal medical support, acute decompensation with severe hypoxic respiratory failure, persistently elevated OI, or severe pulmonary hypertension with cardiac dysfunction [127].

Other considerations in MAS management

Antibiotics. Infants with MAS are often treated with antibiotics. However, the evidence to support this practice is lacking with several RCTs finding no benefit in the routine use of antibiotics in the treatment of MAS [128–131]. In addition, recent systematic and Cochrane reviews found no benefit for the use of antibiotics in MAS and no difference in infection rate [90, 132].

Sedation/paralysis. In MAS and MAS-PPHN, avoid unnecessary stimulation and agitation, and ensure pain is adequately controlled to minimize ventilator asynchrony and pulmonary vasoconstriction [133]. The goal is to alleviate noxious stimuli and agitation to better synchronize CMV, improve the response to HFV, and minimize pulmonary hypertension. Universally, expert consensus supports sedation when needed, titrated to achieve cardiopulmonary stability. Commonly used medications include opioids (morphine and fentanyl), benzodiazepines (midazolam), and central alpha 2 agonists (dexmedetomidine), however no studies to date have explored optimal drug choice in this population. Importantly, routine use of paralysis should be avoided as its use was reported to be associated with increased mortality [134].

RESPIRATORY OUTCOMES AND PROGNOSIS

MAS is associated with short- and long-term complications. In the short term, respiratory complications include air leak syndrome and pneumonia. Broadly, median duration of intubation and ventilation in MAS is three days [12]. Severity of illness correlates with morbidity: one study of 9295 infants with MAS showed that more severe disease was associated with a threefold increase in PPHN, fivefold increase in HIE, and nearly doubled the length of hospital stay [135]. In another large study, 5% of neonates with MAS required oxygen support at 28 days or discharge, and 4.9% experienced seizures [77]. In longer-term follow-up studies, school-age survivors remain at increased risk for pneumonia as well as airway hyperreactivity and alveolar hyperinflation [136]. Further, neurodevelopmental follow-up among MAS survivors reveals common deficits, regardless of the mode of delivery (vaginal versus cesarean) or treatment (conventional ventilation, iNO, or ECMO); one study found a 7% incidence of cerebral palsy and 14% incidence of severe global developmental delay,

while an additional 41% were diagnosed with mild speech delay or hypotonicity without a motor or cognitive abnormality [137].

MAS is also associated with significant mortality, with case fatality rates as high as 40% in past decades, although significantly reduced mortality is seen in the modern era with improvements in perinatal and neonatal management [138]. In a 2009 study of 162,075 term neonates with MAS admitted to a US NICU, mortality was 1.2% [77], with similarly low mortality rates reported in large contemporary studies [12, 13]. Causes of mortality may include progressive respiratory failure, air leak, septic shock, and pulmonary hemorrhage, with severe MAS disease conferring a fourfold risk of death prior to hospital discharge [135]. Compared to survivors, neonates who die from MAS are likely to be smaller, have a lower 5-minute Apgar score, and require more intensive care including mechanical ventilation, surfactant, iNO, antibiotics, steroids, vasopressors, and anticonvulsants [77].

CONCLUSION AND FUTURE DIRECTIONS

Meconium Aspiration Syndrome is a complex condition with variable severity and a wide range of respiratory, cardiovascular, and neurological comorbidities. The pathophysiology of MAS is multifactorial and includes both pulmonary and systemic pathways. While advancements in prenatal and perinatal management have resulted in a decreased incidence of MAS, significant associated morbidity and mortality persist. In the DR, aggressive perinatal suctioning and routine intubation are no longer recommended. In the NICU, treatment focuses on achieving adequate gas exchange while minimizing air trapping and pulmonary injury due to inflammation and atelectasis. The mainstays of therapy are supplemental oxygen, respiratory support, and consideration for surfactant therapy. While studies have explored various ventilatory modalities, evidence to date does not clearly support any singular modality as superior, such that respiratory management should be individually targeted to the patient's pathophysiology, symptom severity, and clinician/unit expertise. Because associated PPHN can meaningfully contribute to morbidity and mortality, early identification and concomitant management of this complication is critical. Moving forward, studies exploring optimal modalities for ventilation and surfactant administration, as well as DR management and new therapeutics may guide future treatment and improve short-and long-term outcomes for patients affected by meconium aspiration.

DATA AVAILABILITY

Sharing of data is not applicable, as this is a review article and new data were created or analyzed.

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AUTHOR CONTRIBUTIONS

AO: conceptualized and designed the study, performed literature review, wrote sections of the manuscript, contributed to Table and Figure development, critically reviewed and revised all sections of the manuscript for important intellectual content, and oversaw the project. CH: conceptualized the manuscript, performed literature review, wrote sections of the manuscript, and critically reviewed and revised all sections of the manuscript for important intellectual content. MC: performed literature review, and wrote sections of the manuscript of the manuscript. HAT: performed literature review and wrote a section of the manuscript. NO: conceptualized and designed the illustrations, and critically reviewed and revised the manuscript for important intellectual content. MKB: conceptualized the manuscript, performed literature review, wrote sections of the manuscript, contributed to Table development, critically reviewed and revised all sections of the manuscript for important intellectual content, and oversaw trainee contributions. All authors approved the final manuscript as submitted and agree to be accountable for all aspect of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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