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Pattern and Risk Factors of Lower Respiratory Illness in Children Who Survived Meconium Aspiration Syndrome

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Abstract

Objective: Meconium aspiration syndrome (MAS) occurs when aspiration of meconium itself or meconium-stained amniotic fluid enters into the airways. The relationship between MAS and the respiratory outcome after recovery from MAS remains unknown. The purpose of this study was to determine the relationship between clinical findings and treatment at birth and the type of LRTI. *Methods:* We extracted the data from Catholic Medical Center's clinical data warehouse and reviewed data from 4 university hospitals. We first selected 1,331 newborns born between March 2016 and February 2021 with diagnostic codes including labor and delivery complicated by fetal stress (distress), intrauterine hypoxia, and neonatal aspiration syndromes. At last, 239 patients who visited the outpatient clinic with diagnoses of pneumonia, acute bronchitis, acute bronchiolitis, and asthma, according to the Korean Standard Classification of Diseases were included in our study. *Results:* We observed a significantly higher number and fraction of eosinophils at birth in the bronchitis group. We also found significantly lower levels of white blood cells in the asthma group. After regression analysis, we found that mechanical ventilation and steroid usage for the treatment of MAS were significantly related to bronchitis and that antibiotics treatment acted as a protective factor for bronchiolitis. *Conclusion:* Laboratory findings and treatment at birth in infants with MAS appear to have an impact on determining LRTI in those who survived MAS.

Keywords

Meconium aspiration syndrome
Bronchitis
Bronchiolitis
Pneumonia
Asthma

1. Introduction

Meconium aspiration syndrome (MAS) is a condition caused by the passage of fetal meconium into the amniotic fluid, which is then aspirated into the fetus' lungs. The symptoms of meconium aspiration syndrome can range from meconium-stained amniotic

fluid to mild to severe respiratory distress, and in some cases, death [1]. Adverse effects of MAS include airway obstruction, impaired gas exchange, pulmonary arterial hypertension, and pneumonia [2].

A recent systematic review reported that surfactant administration in neonates with meconium aspiration syndrome may reduce the severity of the condition and may also reduce the frequency of progression to respiratory failure and the need for extracorporeal membrane oxygenation [3]. Low-quality evidence suggests that steroid administration does not reduce mortality from MAS [1]. Mechanical ventilation is the mainstay of treatment for neonates with meconium aspiration syndrome. Nasal positive pressure ventilation may reduce the need for mechanical ventilation in the first 7 days of life compared to conservative treatment [4]. The clinical prognosis of meconium aspiration syndrome is variable, but despite aggressive treatment, the mortality rate is quite high, ranging from 4%–40% [5].

Infectious and non-infectious respiratory illnesses experienced during neonatal and infancy appear can be outgrown, but they are associated with a decline in lung function during adulthood [2]. In addition, damage to the developing respiratory system in utero may be a determinant of adult lung function [6]. It is thought that birth injury, such as meconium aspiration syndrome, may influence respiratory disease in adulthood, but this has not been proven yet. Therefore, we aimed to identify the lower respiratory tract infection (LRTI) that occurs in children who survive MAS and identify the risk factors.

2. Subjects and methods

2.1. Target population

A retrospective observational study was performed using data from the clinical data warehouse of Catholic Central Medical Center and included neonates born at four university hospitals from March 1, 2016, to February 28, 2021. Of the 1,331 infants born during this period who were diagnosed with O68 fetal stress (desperation), P20 intrauterine hypoxia, and P24 neonatal aspiration syndrome according to the Korean version of the International Classification of Diseases-7 based on the International Classification of Diseases-10, 239 infants were diagnosed with J18 pneumonia of unspecified etiology, J20 acute bronchitis, J21 acute bronchiolitis, or J45 asthma during outpatient follow-up until February 28, 2021. This study was approved by the Institutional Review Board (IRB) of Bucheon St Mary's Hospital (IRB approval number: HC21WIDI0067).

2.2. Blood tests and treatment data

All patients in this study were examined in terms of white blood cell count, eosinophil percentage, eosinophil count, arterial blood pH, and partial pressure of oxygen/carbon dioxide, at birth. The use of mechanical ventilation for the treatment of MAS at birth, steroid use, antibiotic use, surfactant use, and the presence of abnormal chest radiological findings were included in the medical records as well.

3. Statistical analysis

The Pearson chi-square test was used to compare the treatment of MAS between the two groups according to the occurrence of lower respiratory tract diseases, and a Student *t*-test was performed to test the significance of mean values after determining the normal distribution. Logistic regression analysis was carried out to investigate the factors contributing to each type of LRTI. Statistical analysis was performed using SPSS 20.0 (IBM Co., Armonk, NY, USA). A *P-value* of less than 0.05 was considered statistically significant.

4. Result

The study included 239 children, 128 of whom were boys. The mean birth weight of the patient group was 3.23 ± 0.48 kg. The blood test findings at birth and concomitant abnormalities on chest radiographs are

described in Table 1. Mechanical ventilation therapy was used to treat meconium aspiration syndrome in 19 cases, steroids in 43 cases, antibiotics in 192 cases, and surfactants in 18 cases. The types of LRTI that occurred during follow-up were bronchitis in 186 cases, pneumonia in 59 cases, bronchiolitis in 75 cases, and asthma in 55 cases (Table 1).

Table 1. General characteristics of the study population (n = 239)

Characteristic	Value
Male sex	128 (53.6)
Birth weight (kg)	3.23 ± 0.48
Blood test at birth	
White blood cell ($\times 10^4$)	18,140 ± 6,472
Eosinophil ($\times 10^4$)	322.9 ± 330.4
Eosinophil (%)	1.88 ± 1.72
pH	7.37 ± 0.09
PaO_2 (mmHg)	84.24 ± 36.76
$PaCO_2$ (mmHg)	33.91 ± 9.38
SaO_2 (%)	94.20 ± 8.93
Treatment for MAS	
Ventilator	19 (7.9)
Steroid	43 (18.0)
Antibiotics	192 (80.3)
Surfactant	18 (7.5)
Abnormal chest X-ray	108 (61.4)
Lower respiratory tract illness	
Bronchitis	186 (77.8)
Pneumonia	59 (24.7)
Bronchiolitis	75 (31.4)
Asthma	55 (23.0)

Note: Values are presented as number (%) or mean ± standard deviation. Abbreviations: PaO_2, oxygen pressure; $PaCO_2$, carbon dioxide pressure; SaO_2, oxygen saturation; MAS, meconium aspiration syndrome.

4.1. Differences between postnatal blood tests and vital signs and the development of LRTI

The newborn eosinophil count and eosinophil quartile were significantly in the bronchiolitis group (314.73 ± 359.75 cells × 10^4 vs. 241.88 ± 174.72 cells × 10^4, P = 0.043; 2.0% ± 1. 9% vs. 1.44% ± 1.06%, P = 0.034) and the newborn white blood cell count in the asthma group was significantly lower (16,481.40 ± 6,583.20 cells × 10^4 vs. 18,625.61 ± 6,376.92 cells×10^4, P = 0.039). No significant differences were observed in other diseases (Table 2).

4.2. Risk factors for the development of LRTI during postnatal care

The use of mechanical ventilation and steroids as treatment for MAS were associated factors For bronchiolitis, and antibiotics had a protective effect (Table 3). For pneumonia and asthma, there were no significant risk factors (Table 4).

5. Discussion

In this study, we found that among survivors of MAS, children who develop bronchiolitis had a higher number and percentage of eosinophils at birth, and those who develop asthma had a significantly lower white blood cell count at birth. Logistic regression analysis showed that mechanical ventilation therapy and steroid use as treatment for MAS contributed to the development of bronchiolitis, while the use of antibiotics as treatment for MAS was a protective factor in the development of bronchiolitis.

In overseas studies, the frequency of meconium-stained amniotic fluid was 7%–22%, and the incidence of MAS was estimated to be 8% of all newborns [7]. Meconium is known to cause lung injuries, and it was proven to cause chemical interstitial pneumonia in an animal model of MAS using a rabbit model [8]. In addition, animal studies in which meconium was inhaled have shown to cause apoptosis, inflammatory cell infiltration, and increased airway hyperresponsiveness [9-10]. The factors contributing to the pathophysiological damage that occurs in MAS are diverse and have not been fully understood, and empirical treatment is the mainstay of clinical care.

Lung growth is not complete at birth and the number of alveoli increases more than 10-fold over the first 10 years of life. These developing lungs are vulnerable to a variety of injuries such as neonatal

Table 2. Comparison of blood test results performed at birth according to the type of LRTI

Variable	Bronchitis (+) [*n* = 134]	Bronchitis (-) [*n* = 41]	*P*-value	Pneumonia (+) [*n* = 42]	Pneumonia (-) [*n* = 133]	*P*-value	Bronchiolitis (+) [*n* = 56]	Bronchiolitis (-) [*n* = 199]	*P*-value	Asthma (+) [*n* = 39]	Asthma (-) [*n* = 136]	*P*-value
White blood cell ($\times 10^4$)	17,944.26 ± 6,361.07	18,778.26 ± 6,844.26	0.418	18,681.91 ± 7,673.95	17,973.91 ± 6,070.63	0.492	17,841.43 ± 7,380.77	18,279 ± 6,025.79	0.641	16,481.40 ± 6,583.20	18,625 ± 6,376.92	0.039
Eosinophil ($\times 10^4$)	314.73 ± 359.75	241.88 ± 174.72	0.043	253.54 ± 215.45	313.34 ± 357.66	0.226	262.45 ± 220.74	315.10 ± 367.39	0.252	299.77 ± 315. 90	298.22 ± 333.55	0.976
Eosinophil (%)	2.0 ± 1.9	1.44 ± 1.06	0.034	1.70 ± 1.36	1.93 ± 1.82	0.322	1.71 ± 1.40	1.96 ± 1.85	0.283	2.03 ± 1.77	1.83 ± 1.71	0.457
pH	7.37 ± 0.09	7.36 ± 0.09	0.267	7.36 ± 0.10	7.37 ± 0.08	0.681	7.37 ± 0.10	7.37 ± 0.08	0.916	7.37 ± 0.07	7.37 ± 0.09	0.861
PaO_2 (mmHg)	84.50 ± 37.33	83.37 ± 35.23	0.858	87.29 ± 36.98	83.21 ± 36.76	0.512	83.50 ± 31.52	84.58 ± 39.06	0.840	92.92 ± 37.32	81.93 ± 36.39	0.097
$PaCO_2$ (mmHg)	33.22 ± 9.02	35.99 ± 10.21	0.079	34.31 ± 10.41	33.77 ± 9.05	0.732	33.99 ± 10.26	33.87 ± 8.98	0.938	32.16 ± 10.54	34.39 ± 9.01	0.177
SaO_2 (%)	94.61 ± 7.99	92.88 ± 11.48	0.263	95.16 ± 5.67	93.88 ± 9.79	0.396	94.42 ± 10.03	94.10 ± 8.41	0.832	95.57 ± 7.25	93.84 ± 9.32	0.284

Note: Values are presented as number (%) or mean ± standard deviation. Abbreviations: PaO_2, oxygen pressure; $PaCO_2$, carbon dioxide pressure; SaO_2, oxygen saturation; MAS, meconium aspiration syndrome.

Table 3. LRTI with significant risk factors of treatment for meconium aspiration syndrome by logistic regression analysis

Variable	Bronchitis			Bronchiolitis		
	No. (%)	OR (95% CI)	*P*-value	No. (%)	OR (95% CI)	*P*-value
Ventilator	15 (8.12)	5.139 (1.048–25.188)	0.044	6 (8.00)	0.984 (0.271–3.576)	0.981
Steroid	27 (14.52)	0.272 (0.076–0.970)	0.045	14 (18.67)	0.956 (0.262–3.488)	0.946
Antibiotics	38 (20.43)	1.387 (0.438–4.394)	0.579	56 (74.67)	0.352 (0.128–0.968)	0.043
Surfactant	9 (4.84)	0.304 (0.064–1.450)	0.135	9 (12.00)	3.513 (0.793–15.555)	0.098
X-ray	83 (61.48)	1.567 (0.684–3.590)	0.288	33 (58.93)	0.817 (0.395–1.687)	0.585

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 4. LRTI with no significant risk factors of treatment for MAS by logistic regression analysis

Variable	Pneumonia			Asthma		
	No. (%)	OR (95% CI)	*P*-value	No. (%)	OR (95% CI)	*P*-value
Ventilator	3 (5.08)	0.490 (0.090–2.666)	0.409	1 (1.82)	0.240 (0.027–2.165)	0.203
Steroid	8 (13.56)	0.754 (0.184–3.090)	0.695	7 (12.73)	0.686 (0.137–3.425)	0.645
Antibiotics	48 (81.36)	1.182 (0.354–3.946)	0.786	41 (74.55)	0.651 (0.219–1.932)	0.439
Surfactant	3 (5.08)	0.891 (0.149–5.334)	0.900	3 (5.45)	1.594 (0.219–11.603)	0.646
X-ray	28 (66.67)	1.452 (0.669–3.151)	0.346	23 (58.97)	1.011 (0.461–2.215)	0.979

OR, odds ratio; CI, confidence interval.

respiratory distress syndrome, oxygenation, and mechanical ventilation [11]. In this study, we investigated the risk factors at birth for various LRTI in survivors of MAS. We found that bronchiolitis was associated with higher newborn eosinophil counts and eosinophil percentage. Previous studies have found similar results in animal models. In mice, the instillation of meconium into the airways resulted in increased airway hyperresponsiveness, as well as increased lymphocyte/eosinophilic inflammation, which was accompanied by tufted cellularization [12]. An increase in eosinophil/inflammatory progenitor cells in the neonatal period was significantly associated with respiratory disease in the first 24 months of life. This increase in eosinophil/inflammatory progenitor cells is thought to be due to prenatal exposure and the Th2 environment at birth [13].

In this study, a comparison of birth treatments in the bronchiolitis- and non-bronchiolitis-prone groups showed that steroid administration at birth was associated with a lower incidence of bronchiolitis. Previous studies have reported that intravenous methylprednisolone can reduce oxygen requirements and duration of resuscitation in patients with meconium aspiration syndrome [14]. Surfactant administration has been shown to be effective in the treatment of meconium aspiration syndrome. A previous systematic review and meta-analysis found that surfactant administration reduced respiratory failure and the need for extracorporeal membrane oxygenation therapy. Meconium causes modifications in the phospholipids and proteins of surfactants, which disrupts the surfactants' structure and function [15]. However, the mechanisms by which steroid administration at birth is associated with a lower incidence of bronchiolitis in meconium aspiration syndrome remain to be investigated.

In this study, the use of mechanical ventilation as a treatment for MAS was a risk factor for the development of bronchiolitis. In MAS, mechanical ventilation can cause pressure and volume damage, and oxygen therapy can cause an inflammatory response [16]. Previous studies have reported that mechanical ventilation in the neonatal period is a risk factor for hospitalization for bronchiolitis [17]. Severe MAS requiring mechanical ventilation may lead to bronchiolitis, but the design of this study did not allow us to determine the severity. Therefore, further studies are needed to investigate whether mechanical ventilation leads to bronchiolitis in children with MAS.

In this study, we observed a significantly lower white blood cell count at birth in the asthmatic group. Previous studies have reported that MAS is a risk factor for the development of asthma symptoms up to 2 years of age [18]. However, the association between the number of white blood cells at birth and the development of asthma is yet to be studied. Further research may shed light on the association between white blood cell count and progression to asthma.

This study also found an association between antibiotic use in the neonatal period and a reduced incidence of bronchiolitis obliterans. Despite the empirical use of antibiotics as treatment for MAS, systematic reviews and meta-analyses have shown that antibiotic use does not significantly reduce mortality, infection/sepsis, or length of hospital stay [19-20]. Antibiotic treatment in the neonatal period may alter the infant's gut flora, leading to a variety of conditions such as asthma, type 2 diabetes, inflammatory bowel disease, and milk allergy [21]. In addition, children exposed to antibiotics in the neonatal period are more likely to experience asthma exacerbations due to severe viral infections, which means that the frequency of antibiotic prescriptions increases due to impaired defenses against viral infections [22]. Previous studies have reported that antibiotic treatment in the neonatal period is a risk factor for hospitalization for bronchiolitis and bronchiolitis obliterans [17].

A recently published study reported a significant increase in proinflammatory cytokines and the anti-inflammatory cytokine interleukin-10 in the serum of neonates with MAS [23]. In addition, in animal models, cyclooxygenase was increased in MAS rat models,

resulting in an increase in arachidonic acid, which may trigger an inflammatory response [16]. Thus, it appears that the damage experienced in the neonatal period is associated with the development of various LRTIs through an inflammatory response.

The strength of this study is that it examines a range of lower respiratory tract conditions and risk factors in survivors of MAS that have not been investigated to date.

Limitations of the study include the use of clinical data warehouse data, which limits the availability of useful birth information such as birth week and Apgar score, and the use of diagnostic codes to define the study population, which may have resulted in some inaccurate diagnoses. In addition, we followed children for up to five years after birth, which may have contributed to the low number of asthma diagnoses. However, if antibiotic use was associated with bronchiolitis, there may be some cases of asthma diagnosed later in life.

6. Conclusion

In conclusion, clinical findings and the type of treatment received for MAS at birth appear to influence the development of LRTI such as bronchitis, bronchiolitis, and asthma. Future studies are needed to elucidate the long-term effects of neonatal injury.

Disclosure statement

The authors declare no conflict of interest.

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