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Research Article

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Impact of histologic chorioamnionitis on pulmonary hypertension and respiratory outcomes in preterm infants

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Abstract

We aimed to evaluate the association between the presence of histologic chorioamnionitis (HC) and development of pulmonary hypertension (PH) during neonatal intensive care unit (NICU) stay. Data of preterm infants born at 32 weeks of gestation or less were reviewed. The development of PH and other respiratory outcomes were compared according to the presence of HC. Potential risk factors associated with the development of PH during NICU stay were used for multivariable logistic regression analysis. A total of 188 infants were enrolled: 72 in the HC group and 116 in the no HC group. The HC group infants were born at a significantly shorter gestational age and lower birthweight, with a greater proportion presenting preterm premature rupture of membrane (pPROM) > 18 h before delivery. More infants in the HC group developed pneumothorax ($P = 0.008$), and moderate and severe bronchopulmonary dysplasia (BPD; $P = 0.001$ and $P = 0.006$, respectively). PH in the HC group was significantly more frequent compared to the no HC group (25.0% versus 8.6%, $P = 0.002$). Based on a multivariable logistic regression analysis, birthweight ($P = 0.009$, odds ratio [OR] = 0.997, 95% confidence interval [CI] = 0.995–0.999), the presence of HC ($P = 0.047$, OR = 2.799, 95% CI = 1.014–7.731), and duration of invasive mechanical ventilation (MV) > 14 days ($P = 0.015$, OR = 8.036, 95% CI = 1.051–43.030) were significant factors. The presence of HC and prolonged invasive MV in infants with lower birthweight possibly synergistically act against preterm pulmonary outcomes and leads to the development of PH. Verification of this result and further investigation to establish effective strategies to prevent or ameliorate these adverse outcomes are needed.

Keywords

bronchopulmonary dysplasia, inflammation, mechanical ventilation

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Fetal exposure to antenatal inflammation has been studied to induce preterm labor, have diverse effects on innate immune system, and contribute to various neonatal outcomes in preterm infants.[1,2] In particular, histologic chorioamnionitis (HC) is diagnosed based on presence of polymorphonuclear cellular infiltrates and is generally thought to have a superior reflection of antenatal inflammatory response, compared to clinical chorioamnionitis which is identified by characteristic maternal (increased leukocyte counts and C-reactive protein, uterine tenderness and foul odor of vaginal discharge, tachycardia, and fever) or fetal findings (fetal tachycardia).[3] HC has been previously studied for its possible positive or negative effects on the development of lung diseases such as respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) in preterm infants.[4–6]

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In the meantime, there have been few reports on the possible association between antenatal inflammation/chorioamnionitis and pulmonary hypertension (PH), in term infants or in animal models[7,8] but not in preterm infants. PH is one of the most fatal neonatal pulmonary pathologies, and because these infants are thought to have a greater risk of death and a higher chance of respiratory condition exacerbation by an overwhelming infection even after survival, PH should be one of major concerns for clinicians and caregivers. Therefore, in the present study, we aimed to outline the association between HC and respiratory outcomes of preterm infants, with a particular focus on PH, during neonatal intensive care unit (NICU) stay.

Methods

Patient selection and study design

Retrospective data were collected for infants admitted to the NICU of Seoul St. Mary's Hospital from November 2014 to February 2017. Preterm infants born at 32 weeks of gestation or less were included. Infants who did not have their mother's placental pathology results were excluded. Other reasons for exclusion were incomplete data for antenatal history, major congenital anomalies or major intrauterine morbidity, lack of data for the first weeks of life as in outborn patients, and death before the 14th day of life.

Maternal and neonatal characteristics were collected including HC results, preterm premature rupture of membrane (pPROM) hours, maternal underlying morbidities, completion of antenatal steroid (ANS) cycle, other maternal infections (results obtained from microbial tests of vaginal, cerclage tip, amniotic fluid, or placental samples), and basic information concerning gestational age (GA), birthweight, and Apgar scores of the infants. HC was diagnosed when polymorphonuclear cells were present within the amnion or chorion, as previously described by Redline et al.[3] Parameters associated with the respiratory outcomes such as RDS, surfactant instillation doses, pneumothorax, development and severity of BPD, duration of invasive mechanical ventilator (MV), need for home oxygen therapy, and development of PH were also obtained. PH was defined as the use of inhaled nitric oxide (iNO) or sildenafil due to severe oxygenation failure, in accordance with accompanied echocardiographic findings such as tricuspid valve regurgitation with right ventricle enlargement, right-to-left or bidirectional shunt through patent foramen ovale, and/or patent ductus arteriosus. For BPD, we followed the definition based on the most recent NICHD/NHLBI/ORD Workshop summary.[9] Other supplemental data such as neonatal morbidities like hemodynamically significant patent ductus arteriosus (hsPDA, defined as PDA requiring treatment due to clinical symptoms and signs implicating significant left-to-right ductal shunt like need for vasopressors, continued or increasing need for respiratory support, metabolic acidosis, oliguria, feeding intolerance, etc.; the detailed treatment strategy of our unit was fundamentally based on the clinical and echocardiographic criteria previously introduced by McNamara et al.[10] which is described in previous study of ours[11]), intraventricular hemorrhage (IVH) graded according to Papile's criteria,[12] and necrotizing enterocolitis (NEC) $\geq$ stage 2 of modified Bell's criteria,[13] and hospital course such as the length of stay, postmenstrual age (PMA) at discharge, and body weight at discharge were collected.

The above-collected parameters were compared between two groups depending on the presence of HC: HC group versus no HC group. Then potential risk factors—including HC—associated with the development of PH, which was the main outcome of our interest, were used in multivariable regression analysis model.

Statistical analysis

Continuous variables and categorical variables were compared between subgroups using Student's t-test and chi-square or Fisher's exact tests, as appropriate. Multivariable logistic regression analysis was executed in a backward conditional manner. A P value < 0.05 was considered statistically significant.

Ethical approval

The study was approved by the institutional review board of Seoul St. Mary's Hospital.

Results

A total of 259 infants of GA ≤ 32 weeks were admitted to the NICU. Of these, 71 infants were excluded for the following reasons: (1) transferred in from other hospitals after 7th day of life (n = 11); (2) died within the first 14 days of life (n = 10); (3) major congenital anomaly or critical prenatal condition like hydrops fetalis (n = 9); (4) severe hypoxic ischemic encephalopathy (HIE) at birth (n = 1); (5) uncertain GA due to obscure antenatal history (n = 1); and (6) no histologic results for placenta or incomplete maternal data (n = 39). Thus, 188 infants were enrolled and divided into two groups according to the presence of HC (72 infants in the HC group versus 116 infants in the no HC group). The patient enrollment scheme is depicted in Fig. 1.

The basic demographics of the infants are described in Table 1. Infants in the HC group were significantly smaller in terms of GA and birthweight (both $P < 0.001$) and Apgar scores lower ($P = 0.002$ for 1-min Apgar and $P = 0.020$ for 5-min Apgar) compared to the no HC group. A significantly greater portion of infants in the no HC group were small-for-gestational-age (SGA), male, and had been delivered via Cesarean section. A greater percentage of the HC group infants had presented with pPROM > 18 h before delivery. Regarding maternal characteristics, a greater portion of mothers had presented with hypertension ($P = 0.027$) in the no HC group and had positive culture results for

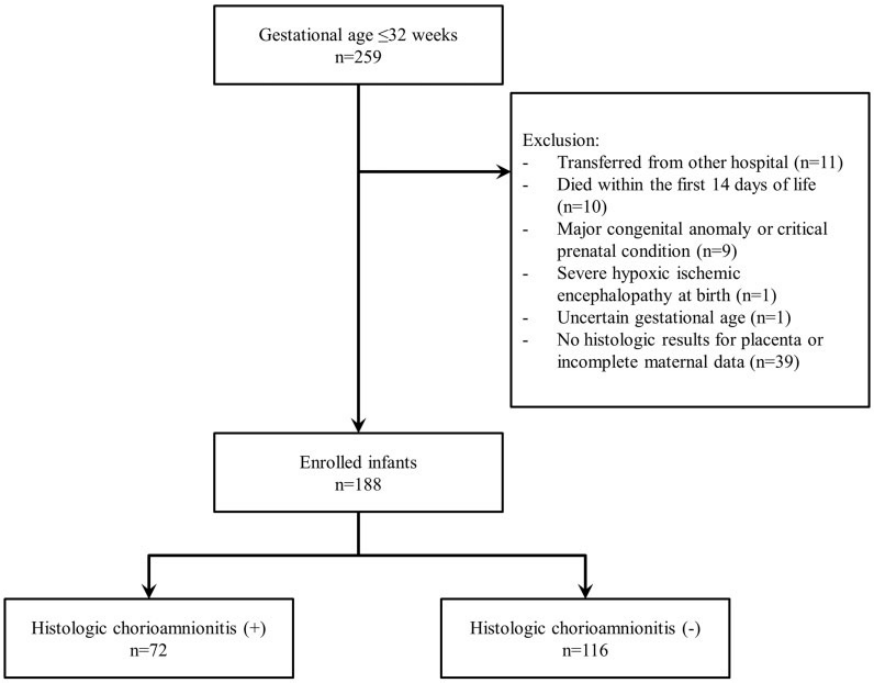

Fig. 1. The patient enrollment scheme of the study.

Ureaplasma urealyticum from vaginal samples ($P = 0.005$). The completion of antenatal steroid cycle tended to be more prominent in the no HC group but did not show statistical significance.

Respiratory outcomes of the enrolled infants during NICU stay were compared (Table 2). Greater percentages of (but not statistically significant) infants in HC group had RDS and used ≥ 2 doses of surfactant compared to the no HC group. Only two infants (1.7%) in the no HC group developed pneumothorax while eight (11.1%) in the HC group did ($P = 0.008$). Regarding BPD, almost a twofold percentage of the infants in the HC group presented both moderate and severe BPD compared to the no HC group ($P = 0.001$ and 0.006, respectively). The duration of invasive MV was also significantly longer in the HC group infants (median 17 days versus 4 days, $P = 0.022$). A significantly greater portion of HC group infants had used postnatal steroid for treatment of BPD (41.7% versus 24.3%, $P = 0.013$) and required home oxygen treatment (40.6% versus 24.5%, $P = 0.026$). PH in the HC group was also significantly greater in proportion when compared to the no HC group (25.0% versus 8.6%, $P = 0.002$).

A supplemental analysis for outcomes other than respiratory morbidities was also executed (Table 3). Overall morbidities and mortality did not show statistical significance between the HC and no HC groups. Only the length of hospital stay presented a significant difference, but PMA or body weight at discharge did not satisfy statistical disparity.

Since our greatest interest was whether HC was potentially associated with the development of PH in preterm infants, variables—including HC—with known or possible association with PH development during NICU stay were included in the multivariable logistic regression analysis model (Table 4). Among the factors recruited for association with PH development, birthweight ($P = 0.009$, odds ratio [OR] = 0.997, 95% confidence interval [CI] = 0.995–0.999), the presence of HC ($P = 0.047$, OR = 2.799, 95% CI = 1.014–7.731), and duration of invasive MV > 14 days ($P = 0.015$, OR = 8.036, 95% CI = 1.051–43.030) were significant factors.

The clinical characteristics of the PH infants during NICU stay are as follows. Twenty-eight infants received treatment for PH at any time during NICU stay. PH was diagnosed as early as the first day of life and as late as the 216th day of life (median = 11th day of life). All but one infant received inhaled NO therapy. Six infants received sildenafil (2–3 mg/kg per dose every 8–12 h) and nine infants received intravenous milrinone (0.25–0.75 mcg/kg/min) titrated according to clinical symptoms and echocardiographic findings. Twenty-four of the PH infants had severe BPD; 17 of these required home oxygen therapy. Five infants died before discharge from NICU and two infants who had failed repeated trials of extubation were transferred to the pediatric intensive care unit on ventilator.

Discussion

Based on our results, respiratory morbidities, including PH, were significantly more frequently encountered in infants with HC. Furthermore, birthweight, HC, and duration of invasive MV > 14 days were significant factors associated with the development of PH during NICU stay.

Table 1. Demographics of the enrolled infants according to the presence of histologic chorioamnionitis (HC).

	HC (n = 72)	No HC (n = 116)	*P* value
Gestational age (weeks)	27.6 (25.5–29.8)	30.4 (28.6–31.8)	<0.001
Birthweight (g)	1058 (803–1309)	1400 (953–1719)	<0.001
1-min Apgar	2 (1–4)	4 (2–5)	0.002
5-min Apgar	6 (4–7)	6 (5–8)	0.020
SGA	4 (5.6)	21 (18.1)	0.014
Male	30 (41.7)	66 (56.9)	0.042
C/S delivery	60 (83.3)	109 (94.0)	0.019
pPROM > 18 h	22 (30.6)	17 (14.7)	0.009
Mother age (years)	32 (30–36)	33 (31–35)	0.510
Maternal diabetes	5 (6.9)	4 (3.4)	0.307*
Maternal hypertension	8 (11.1)	28 (24.1)	0.027
Placental abruption	6 (8.3)	8 (6.9)	0.715
Maternal ureaplasma	55 (76.4)	65 (56.0)	0.005
Antenatal steroid	26 (36.1)	56 (48.3)	0.102
Other maternal infection	21 (29.2)	21 (18.1)	0.077

Data are presented as median (interquartile range) or n (%).
*Fisher's exact test.
C/S, Cesarean section; HC, histologic chorioamnionitis; pPROM, premature preterm rupture of membrane; SGA, small for gestational age.

Table 2. Respiratory outcome of the enrolled infants during NICU stay according to the presence of histologic chorioamnionitis (HC).

	HC (n = 72)	No HC (n = 116)	*P* value
RDS	66 (91.7)	96 (82.8)	0.085
Surfactant ≥ 2 doses	10 (13.9)	13 (11.2)	0.585
Pneumothorax	8 (11.1)	2 (1.7)	0.008*
Moderate-to-severe BPD	44 (61.1)	41 (35.3)	0.001
Severe BPD	29 (40.3)	25 (21.6)	0.006
Postnatal steroid	30 (41.7)	28 (24.1)	0.013
Invasive MV (days)	17 (2–50)	4 (2–21)	0.022
Invasive MV > 14 days	36 (50.0)	33 (28.4)	0.003
Home oxygen therapy†	26 (40.6)	27 (24.5)	0.026
PH during NICU stay	18 (25.0)	10 (8.6)	0.002

Data are presented as median (interquartile range) or n (%).
*Fisher's exact test.
†Sixty-four infants in the HC group and 110 infants in no HC group were compared (patients who have expired or transferred to other hospital were excluded).
BPD, bronchopulmonary dysplasia; HC, histologic chorioamnionitis; MV, mechanical ventilation; NICU, neonatal intensive care unit; PH, pulmonary hypertension; RDS, respiratory distress syndrome.

HC is known to be present in 45–60% of very low birthweight (VLBW) infants and increases the risk of spontaneous preterm labor and subsequent preterm birth.[14–16] HC was present in approximately 38.1% of the infants enrolled in our study, which is rather lower than the above-mentioned incidence. The lower frequency may have been due to the enrollment criteria: we included infants based on GA criterion and not birthweight criterion. Shorter GA and smaller birthweight in the HC group infants are features consistent with literature, and they would have contributed to the lower Apgar scores. HC has been shown to be associated with poor fetal growth or early postnatal growth, yet the association has been inconsistent according to studies.[17,18] The predominance of maternal hypertension[19] may have been related with the greater portion of SGA infants in the no HC group in our study. More HC group infants had been born to mothers with positive *Ureaplasma* culture results.[20]

Based on our results, though insignificant, a greater percentage of HC group infants tended to have been diagnosed

Table 3. Other neonatal morbidities, mortality, and hospital course.

	HC (n = 72)	No HC (n = 116)	*P* value
hsPDA	21 (29.2)	25 (21.6)	0.238
Severe IVH	13 (18.1)	20 (17.2)	0.908
Cystic PVL	5 (6.9)	9 (7.8)	0.836
NEC ≥ stage 2	8 (11.1)	7 (6.0)	0.212
Death	4 (5.6)	4 (3.4)	0.485*
Hospital stay (days)†	63 (46–92)	45 (30–62)	0.001
PMA at discharge (weeks)†	36.9 (35.3–40.3)	36.6 (35.3–38.4)	0.147

Data are presented as median (interquartile range) or n (%).
*Fisher's exact test.
†Sixty-four infants in the HC group and 110 infants in no HC group were compared (patients who have expired or transferred to other hospital before discharge were excluded).
HC, histologic chorioamnionitis; hsPDA, hemodynamically significant patent ductus arteriosus; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PMA, postmentrual age; PVL, periventricular leukomalacia.

Table 4. Multivariable logistic regression analysis for evaluation of potential risk factors associated with development of PH.

	P value	Odds ratio	95% CI
Gestational age (weeks)	0.649	0.873	0.486–1.568
Birthweight (g)	0.009	0.997	0.995–0.999
HC	0.047	2.799	1.014–7.731
SGA	0.903	1.145	0.128–10.230
hsPDA	0.888	1.080	0.371–3.147
Pneumothorax	0.628	1.438	0.330–6.260
Invasive MV > 14 days	0.015	8.036	1.501–43.030
Moderate-to-severe BPD	0.290	2.695	0.429–16.939

BPD, bronchopulmonary dysplasia; HC, histologic chorioamnionitis; hsPDA, hemodynamically significant patent ductus arteriosus; MV, mechanical ventilation; PH, pulmonary hypertension; SGA, small for gestational age.

as having RDS or have received ≥ 2 doses of surfactant instilled endotracheally. Through animal studies, prenatal inflammation has been known to cause lung maturation,[21,22] and Watterberg et al.[23] described that the incidence of RDS in preterm infants exposed to chorioamnionitis had decreased. However, some papers raised the possibility of alteration of surfactant composition, dysregulation of modulatory function against surfactant inhibitory proteins, and decreased responses to exogenous surfactant replacement therapy.[9,24] Furthermore, the difference in GA and birthweight between the two groups may have contributed to the tendency of infants in the HC group to have experienced more severe respiratory failure. In addition, despite low frequency, an approximately fourfold more portion of HC group infants in our study had developed pneumothorax. Requirements for greater respiratory support for severe respiratory condition and more fragile lung parenchyma due to inflammation may be related to the difference in incidence of pneumothorax between the two groups.

We also identified from our study results the difference in duration of invasive MV and severity of BPD depending on the presence of HC. According to a recent systematic review, although less striking after adjusting by GA and birthweight, HC and BPD had still shown an association.[25] Alveolar and vascular simplification caused by endotoxin-induced chorioamnionitis is associated with pulmonary inflammation, and becomes vulnerable to further inflammation by various postnatal second hits such as resuscitation, oxygen toxicity, prolonged invasive mechanical ventilation, and infection.[26,27] Ikegami et al. showed that antenatal exposure to endotoxin augmented the postnatal inflammation in the lungs of ventilated preterm lambs.[28] In addition to such experimental findings, several publications have presented the possible link between the presence of chorioamnionitis and an increased risk of BPD/PH.[5,29,30] Our study results of a higher prevalence of moderate and severe BPD and longer duration of invasive MV in the HC group infants are consistent with such works. That a greater portion of the HC group infants had received postnatal steroid for BPD treatment and home oxygen therapy are also in line with the prevalence of BPD in these group of infants.

Furthermore, this explanation may be extended to the higher prevalence of PH in HC group infants in our study. PH can develop at the early (within 7–14 days based on previous literature[31,32]) or late (variously defined in literature, but the onset generally described to be at weeks to months of life[33,34]) stage of life in preterm infants. Kallapur et al.[35] stated that after antenatal inflammation aroused by intra-amniotic endotoxin exposure, medial smooth muscle hypertrophy and concomitant adventitial layer remodeling changes of small pulmonary arterial walls were observed in preterm lambs. Polgalse et al.[8] showed that the intra-amniotic-lipopolysaccharide-injected preterm lambs exhibited PH-consistent features like pulmonary vascular remodeling leading to increased pulmonary vascular resistance, hampered pulmonary blood flow, and right-to-left shunting through ductus arteriosus. Such vascular remodeling due to the inflammatory network effect of versatile cytokines increase the susceptibility to PH genesis in the early days of preterm infants.[1] In addition, a combination of discordant lung development and prolonged invasive MV would have had synergistic detrimental effects on the preterm lungs, relating to BPD[31,32] and/or PH in the later days in NICU. Mourani et al.[36] described that preterm infants who had experienced PH during the first seven days of life were at a greater risk of developing a more severe grade of BPD and PH at 36 weeks PMA. This is consistent with our postulation that antenatal inflammation would have a role in priming the development of BPD due to disturbed angiogenesis and alveolarization, which can sequentially be aggravated by postnatal events. Likewise, in the multivariable logistic regression analysis, not only was birthweight a significant factor as described in previous studies,[31,33] but HC—which would be the priming factor of aberrant pulmonary genesis and structuralization—and duration of invasive MV are typical examples of postnatal second hit and were also significant risk factors associated with the development of PH.

On the other hand, Tang et al.[37] demonstrated that intra-amniotic endotoxin injection induced PH-like changes in infant rat alveoli and pulmonary vasculature, which in turn was modulated by moderate postnatal hyperoxia. In contrast, severe postnatal hyperoxia further worsened the aberrancy of pulmonary alveolar and vascular structure. Therefore, dose-dependent effects of antenatal inflammation and hyperoxia should be further studied and appropriately interpreted in human BPD and PH.

Meanwhile, besides HC, a placental pathology finding like maternal vascular underperfusion (MVU) has emerged as another important factor potentially associated with the development of BPD and PH. Several reports enlightened the possible relationship of placental underperfusion and being SGA with the development of BPD and PH.[38–40] However, we were not able to directly analyze this relationship, because the description of MVU in the retrospectively collected data was not detailed enough to include MVU in our analysis. Instead, BW:PW (birthweight-to-placental-weight) ratio, which in part is reflective of the placental perfusion status,[41] was compared depending on the development of PH, and it was significant (median [interquartile range] = 2.255 [1.933–2.772] versus 3.098 [2.649–3.740], $P < 0.001$, data not shown).

In turn, being SGA was not associated with the development of PH in the multivariable analysis of our study. The cohorts in the previous publications[38–40] were somewhat smaller in GA (<29–30 weeks compared to < 33 weeks in our study) and this difference might have contributed to the disparity between our and their findings. In addition, Nyp et al.[42] reported that beyond being SGA at birth, impairment in linear and head circumference growth was associated with moderate-to-severe BPD. Therefore, being SGA at birth solely may not be enough when discussing

BPD and PH. Furthermore, according to Lio et al.,[43] the risk of BPD increased dramatically in SGA preterm infants given that placental insufficiency is the major cause of low birthweight. However, as mentioned above, the exact analysis involving placental findings of MVU or prenatal Doppler findings (as in Lio et al.'s study) were not included in our study. Instead, the BW:PW ratio was included and it did not significantly differ depending on being SGA (data not shown). Therefore, although the reason for a lack of association between being SGA and the development of severe BPD or PH cannot be concretely determined, the most probable explanation would be that the cause of SGA in our cohort may not be solely attributable to placental underperfusion.

Our study shares limitations of other retrospective publications for the lack of prospective nature and restricted number of enrolled infants, and it is yet not ripe to extrapolate our study results to other units before obtaining validation from more large-scale prospective studies. Since it was a study based on medical record review, we were not able to assess actual numerical values of various proinflammatory cytokines that potentially are associated with the severity of antenatal inflammation nor histologic lung vascular structure concerning the progression of PH. However, we believe that risk assessment for developing early or late PH and BPD, which are each one of the most difficult-to-treat-well and fatal newborn diseases, would be meaningful for both the parents and caregivers to predict, understand, discuss, and prepare how to handle adverse future prognosis.

In conclusion, HC is possibly associated with development of PH during NICU stay. In preterm infants with lower birthweight, a longer duration of invasive MV potentially acts together with HC in a complicated manner and lead to developing PH in preterm infants. Insights into this association should encourage future investigations with a larger cohort of infants in a prospective manner, to verify our results, and hopefully to establish more tailored, effective strategies to prevent, mitigate, or treat adverse consequences due to inflammation.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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