

## Original Article



# Contact Investigation for Twins With Congenital Tuberculosis in the Neonatal Intensive Care Unit

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## ABSTRACT

**Purpose:** Congenital tuberculosis (TB) is difficult to diagnose owing to its non-specific symptoms. Delayed diagnosis increases the risk of nosocomial infections. We examined the TB status of infants and healthcare workers who were in proximity to preterm twins diagnosed with congenital TB 63 days after birth and 48 days after admission to the neonatal intensive care unit (NICU).

**Methods:** Contact investigations were conducted on 24 staff members and 35 infants who had contact with the twins with congenital TB.

**Results:** Two of the exposed infants, both of whom had received the Bacille Calmette–Guérin vaccine, had positive tuberculin skin test results. Four of the 24 exposed staff members had positive interferon-gamma release assay (IGRA) test results before exposure and were not re-tested after exposure; the remaining 20 had negative IGRA test results. All exposed staff members and infants had normal chest radiographic findings.

**Conclusions:** Although transmission of TB in the NICU is unusual, it can occur. These results support the need for a systematic investigation of the TB status of exposed infants, their family members, and healthcare workers.

**Keywords:** Tuberculosis; Contact investigation; Neonatal intensive care unit

## INTRODUCTION

Congenital tuberculosis (TB) is a rare condition. Before 1995, congenital TB was reported in 358 case,<sup>1)</sup> and 110 cases were reported between 1996 and 2009 worldwide.<sup>2)</sup> A small number of congenital TB cases have also been reported in Korea.<sup>3-5)</sup> Congenital TB often presents with non-specific symptoms; therefore, its diagnosis is often delayed.<sup>6)</sup> If undetected in hospitalized patients, it can spread to other patients and the healthcare staff. TB transmissions can occur in exposed medical staff and infants when cases of congenital TB are present in the neonatal intensive care unit (NICU).<sup>7)</sup> We present a case of twins diagnosed with congenital TB 48 days after admission to our NICU and describe the screening and epidemiological investigations performed in the infants and healthcare workers who had contact with the twins.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Author Contributions

Conceptualization: Yoo MH, Cho HM; Data curation: Yoo MH, Cho HM, Kim KS, Kim YW, Kim EY, Jang HI, Kim Y; Formal analysis: Yoo MH, Cho HM, Kim KS, Kim YW, Kim EY, Jang HI, Kim Y; Investigation: Yoo MH, Cho HM; Project administration: Yoo MH, Cho HM; Supervision: Cho HM, Kim KS, Kim YW, Kim EY, Jang HI, Kim Y; Visualization: Yoo MH; Writing - original draft: Yoo MH; Writing - review & editing: Yoo MH.

## MATERIALS AND METHODS

We have reported this case in a previous study.<sup>8)</sup> A Ugandan mother gave birth to twins via a caesarian section after 30 weeks of gestation. The twins were transferred to our NICU 15 days after birth because of hospital expenses. The first twin (birth weight, 1,590 g) had no abnormalities on physical examination, no specific symptoms suggestive of TB, and normal chest radiographic findings at the time of admission. On the 21st day after birth (the 6th day of hospitalization), tachypnea, apnea, and tachycardia were observed. On the 24th day, chest radiography showed increased haziness in both lungs, which worsened despite antibiotic treatment. The first twin developed a fever on the 43rd day that persisted until the 65th day after birth.

Sixty-three days after giving birth, the twins' mother visited the emergency room at another hospital complaining of fever and loss of consciousness and was diagnosed with TB meningitis via cerebrospinal fluid examination. On the same day, the second twin, who had previously been discharged from the NICU, also developed a fever and was readmitted to our hospital. Chest radiography revealed consolidation in the right upper and middle lobes and numerous tiny nodular densities in both lungs. Acid-fast bacilli staining, polymerase chain reaction using sputum samples, and culturing of gastric fluid revealed the presence of *Mycobacterium tuberculosis* in both twins. *M. tuberculosis* obtained from the samples from both the mother and twins was cultured, and no resistance to anti-TB drugs was observed. The twins were diagnosed with congenital TB, started on anti-TB treatment, and placed in respiratory isolation by the medical staff on day 63 post-birth (48 days after admission). A multidisciplinary team was assembled to investigate and manage suspected outbreaks and prevent further transmission. To determine the presence of nosocomial infections, a contact study was conducted on the infants who were hospitalized with the twins in the NICU and the healthcare staff members and visitors who had contact with the twins.

All exposed infants underwent physical examination and chest radiography. Those aged <3 months (corrected age of 3 months) were administered isoniazid (INH) at a dosage of 10 mg/kg/day. A tuberculin skin test (TST) was performed 3 months after the last day of potential exposure or 3 months after the expected date of delivery (whichever occurred later). All the exposed staff members underwent chest radiography and interferon-gamma release assay (IGRA).

The Institutional Review Board of Kwangju Christian Hospital approved the study (approval number: KCHIRB-RE-2022-006). The board waived the requirement for informed consent.

## RESULTS

A total of 35 infants (21 boys and 14 girls) were exposed to the twins in the NICU for at least 24 hours (**Table 1**). The exposed infants had a mean NICU stay of 16.8 days. The NICU has a total of 15 beds. In the NICU, the air is exchanged 12 times/h using high-efficiency particulate filters, and fresh air is circulated twice per hour.

The first twin was placed in an incubator from days 15–38 post-birth and in a bassinet outside the incubator from days 39–42. On day 43, the first twin was transferred from the NICU to an isolation room owing to the development of a fever. The second twin was in an incubator from days 15–30 post-birth and outside the incubator from days 31–37. The second twin was

**Table 1.** Characteristics of infants exposed to the newborn twins in the neonatal intensive care unit

Variables	Exposed infants (n=35)
Sex (M/F)	21/14
Gestational age (wk)	35.4
Prematurity	23 (65.7)
BCG vaccination	27 (77.2)
Contact days	16.8
Positive TST result	2 (5.7)

Values are presented as number (%).

Abbreviations: BCG, Bacille Calmette–Guérin; TST, tuberculin skin test.

discharged from the NICU on day 37. Among the 35 infants who had come in contact with the twins in the NICU, 10 were exposed when the twins were outside the incubators.

Nasal continuous positive airway pressure was applied to the first twin on days 21–25 and 31–37 post-birth; the second twin did not require oxygen therapy while in the NICU. All medical equipment used for the twins, including feeding tubes, suction tips, and ventilator accessories, were individually used and disposable, and each incubator had its own oxygen supply device.

Of the 35 exposed infants, 27 (77.2%) had received the Bacille Calmette–Guérin (BCG) vaccine, whereas 8 (22.8%) of the infants did not receive it. Two of the 27 vaccinated infants had an 11-mm induration in a TST and were diagnosed to be infected with *M. tuberculosis*. These infants underwent chest radiography 6, 12, and 18 months after the first screening, and all results were normal. They completed 9 months of INH treatment. The 8 infants who had not been vaccinated had an induration size of <5 mm. The ten infants exposed to the twins while the twins were outside the incubator had normal TST results.

Twenty-four staff members (10 doctors and 14 nurses) had contact with the twins. Hospital personnel working in the NICU undergo yearly IGRA tests to check for latent TB infection. Four staff members (2 doctors and 2 nurses) had positive IGRA test results before exposure to the twins; therefore, only chest radiography was performed in this group. The remaining 20 staff members underwent both procedures. The chest radiographs were normal for all 24 staff members, and the IGRA test results were negative for the 20 staff members who took the test after exposure (**Table 2**).

The twins' father had a positive IGRA test result but no clinical symptoms or chest radiographic abnormalities suggestive of TB. He was treated with INH (300 mg/day) for 9 months. During the exposure period, NICU personnel were restricted from visiting guardians because the coronavirus disease 2019 pandemic was ongoing. Therefore, the guardians were considered to have no contact and were not investigated.

**Table 2.** TST and IGRA results for the exposed infants and healthcare staff

Groups	CXR	IGRA	TST	LTBI
Infants (n=35)	35/35 negative	N/A	2/35 positive	2
HCS (n=24)	24/24 negative	20/20 negative	N/A	0

Abbreviations: HCS, health care staff; CXR, chest X-ray; IGRA, interferon-gamma release assay; TST, tuberculin skin test; LTBI, latent tuberculosis infection; N/A, not applicable.

## DISCUSSION

Congenital TB is often difficult to diagnose owing to its nonspecific symptoms. The most common clinical signs are hepatomegaly (75%), dyspnea (72%), fever (48%), lymphadenopathy (38%), abdominal distension (24%), lethargy or irritability (21%), ear discharge (17%), and skin eruptions (14%).<sup>9)</sup> These symptoms are similar to those of more common neonatal diseases, such as bacterial sepsis and congenital viral infections.<sup>10)</sup> For this reason, up to half of congenital TB cases are initially diagnosed as other diseases,<sup>11)</sup> and nosocomial infections can occur before TB is finally diagnosed. Several reports have described the exposure of infants to TB in NICUs.<sup>7,12,15)</sup>

Transmission of nosocomial infections from congenitally infected infants to others is rare. In general, infants are poor transmitters of TB because they do not have a forceful cough.<sup>14)</sup> In rare instances, TB transmission may occur through close contact with infant secretions. A case in which nosocomial infection may have resulted from inadequate disinfection of respiratory equipment in the NICU has been reported.<sup>7)</sup> In our study, 2 infants, both of whom had received the BCG vaccine, had an 11-mm induration in a TST and were diagnosed with latent TB infection. According to the Korean Tuberculosis Guidelines, an induration of  $\geq 5$  mm and  $\geq 10$  mm in a TST is considered indicative of *M. tuberculosis* in BCG-vaccinated and unvaccinated individuals, respectively.<sup>16)</sup> However, when this criterion is used, the false-positive rate can be as high as 8.5% in BCG-vaccinated individuals.<sup>17)</sup> The twins did not have laryngeal TB or endotracheal TB, which are known to be highly contagious. Nasal continuous positive airway pressure was applied to the first twin on days 21–25 and 31–37 post-birth; the second twin did not require oxygen therapy while in the NICU. Aerosol-generating procedures were also performed for a short period. The twins did not show respiratory symptoms such as cough during the majority of NICU stay period. The 10 infants exposed to the twins when they were outside the incubator showed normal TST results. These results suggest that the contagion levels of the twins were low. Two infants treated for latent TB infection were admitted to the NICU while the twins were in the incubator. It is possible that the 2 infants treated for latent TB in our study showed false-positive results.

Transmission of TB from infants with congenital infections to healthcare workers has been documented.<sup>7,14,15)</sup> Aerosol-generating procedures performed in the NICU, such as the suctioning of infected infants, are thought to be an important cause of infection among healthcare workers.<sup>15)</sup> In addition to these procedures, a high bacterial load and respiratory support using a high-frequency oscillatory ventilator with unfiltered exhaust also increase the rate of transmission.<sup>14)</sup>

In conclusion, when congenital TB occurs in the NICU, it is necessary to investigate the exposed staff members and infants as soon as possible while considering the possibility of nosocomial infection. In our study, the risk of transmission was minimal but not negligible. Our results support the need for a systematic approach to investigate the TB status of exposed infants, their family members, and healthcare workers.

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## 요약

**목적:** 선천 결핵은 비특이적 증상을 보이는 경우가 많아 진단이 지연되는 경우가 흔하다. 진단이 지연되면 함께 입원하고 있는 신생아와 의료 종사자에게 결핵이 전파될 가능성은 높아진다. 미숙아로 태어나 신생아집중치료실에 입원해 있던 쌍둥이들이 출생 후 63일, 입원 후 48일째에 선천 결핵으로 뒤늦게 진단되었다. 이에 본 연구에서는 쌍둥이들과 입원 기간 중 함께 접촉했던 신생아 및 의료 종사자들에게 결핵의 전파 여부를 조사하였다.

**방법:** 선천 결핵으로 진단된 쌍둥이와 접촉한 의료 종사자 24명과 신생아 35명을 대상으로 결핵 접촉자 검진을 실시하였다.

**결과:** 쌍둥이들과 접촉한 신생아 35명 중에서 Bacille Calmette-Guérin 백신 접종을 받았던 신생아 중 2명은 투베르쿨린 피부 검사 결과 양성 반응을 보였다. 24명의 의료 종사자 중 4명은 쌍둥이와 접촉하기 이전에 이미 인터페론-감마 방출 분석(interferon-gamma release assay, IGRA) 검사 결과가 양성이었다. 이들을 제외하고 나머지 20명을 대상으로 IGRA 검사를 시행하였고 모두 음성이었다. 쌍둥이와 접촉한 모든 의료 종사자와 신생아들은 흉부 방사선 검사에서 정상이었다.

**결론:** 선천 결핵이 신생아집중치료실에서 발생되었을 때 드물지만 결핵의 전파가 가능하므로 접촉한 신생아, 가족 및 의료종사자에 대한 결핵 접촉자 검진은 반드시 필요하다.