Disseminated tuberculosis was diagnosed at the autopsy of a 65-day-old premature infant who died in a 52-bed neonatal intensive care unit (NICU). Both parents and one sibling had previously had positive tuberculin skin tests (TSTs); none had active pulmonary tuberculosis, but a second sibling had hilar adenopathy. Congenital transmission was confirmed by isolation of Mycobacterium tuberculosis from the mother’s endometrium and the infant’s lung tissue. Both strains were identical by DNA restriction fragment analysis. TSTs were performed on 14 neonates, 27 NICU visitors, 11 contacts of the family, and 260 health care workers. TST conversion occurred in two nurses (0.8%); both had normal chest radiographs and received isoniazid therapy. Exposed neonates had negative chest radiographs, had negative gastric aspirates for acid-fast bacilli, and received isoniazid preventive therapy. Diagnosis of congenital tuberculosis requires a high index of suspicion. Transmission of tuberculosis in the NICU setting is unusual but can occur.
Table 1. Summary of tuberculin skin test results for persons exposed to an infant with tuberculosis that was diagnosed after death.

<table>
<thead>
<tr>
<th>Persons exposed to infant</th>
<th>Tested</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU infants</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Visitors</td>
<td>27</td>
<td>4*</td>
</tr>
<tr>
<td>Health care workers</td>
<td>260</td>
<td>2† (0.8%)</td>
</tr>
</tbody>
</table>

NOTE. NICU = neonatal intensive care unit.
* Positive for unknown duration.
† Tuberculin skin test conversion.

Rounding these areas. The burden of organisms was greatest in the lungs and mediastinal lymph nodes; smaller areas of necrosis and fewer acid-fast bacilli were seen in other organs, including the liver, spleen, adrenal glands, and mesenteric lymph nodes. Radiographs of both the lungs and the liver failed to demonstrate any calcifications of Ghon complexes. Culture of lung tissue yielded *Mycobacterium tuberculosis* susceptible to isoniazid, rifampin, ethambutol, streptomycin, and pyrazinamide.

The placenta was examined after the postmortem diagnosis of tuberculosis was established for the baby. The placenta showed focal subchorionic acute inflammation but no evidence of granulomatous disease. Acid-fast bacilli were not seen.

Results

Epidemiological Data

When the postmortem diagnosis of tuberculosis was initially determined for this baby, the route of transmission to the infant was not known. The degree and duration of possible contagion to others were also unknown. The period of maximum infectiousness probably occurred during the last 20 days of life, when the baby was most severely ill and had been moved from an enclosed incubator to an open bed. A systematic approach was taken to determine the source of infection and the extent of exposure among other neonates, visitors, and health care workers [2].

Community physicians and parents of all NICU babies were notified, and advice was provided regarding screening, prophylaxis or treatment, and long-term monitoring. The county health department was notified and assisted with screening the majority of the exposed neonates and visitors. Results of the Mantoux tuberculin skin tests (TSTs) of the neonates, visitors, and health care workers are summarized in table 1.

Investigation of the Exposed Infants

Exposure among other infants in the NICU was defined as presence in the same room as the index case for at least 24 hours at any time since the birth of the index case. Exact proximity to the index case within the room was not further defined. Fourteen babies fulfilled the criteria for exposure. Exposed babies still in the NICU had TSTs performed, and three early morning gastric aspirates were obtained from each infant for mycobacterial culture. All exposed infants received preventive therapy with isoniazid (10–15 mg/[kg·d]) and pyridoxine (2 mg/d) orally for 6 months. Tests of liver function, including aspartate and alanine aminotransferase levels and values for total bilirubin and alkaline phosphatase, were performed to monitor for isoniazid toxicity. None of these babies had a positive initial TST, abnormal liver function tests, or positive culture results. Chest radiographs were not obtained specifically to look for tuberculous lung involvement.

Babies already discharged from the NICU had chest radiography and a TST performed, and follow-up was arranged through the health department and the primary pediatrician. These babies also received isoniazid preventive therapy for 6 months, and liver function was not monitored unless the infant...
had underlying liver disease. Initial TSTs were negative, and none of the chest radiographs showed tuberculous disease.

TSTs were repeated 3 months after the initial TST; babies were 6–7 months old at this time. Of 10 infants for whom results were available, all had negative follow-up TSTs.

Investigation of Visitors to the NICU

All families of the 14 exposed NICU babies were notified by phone and letter and advised to have TSTs performed at the health department initially and 3 months later. If a TST was positive, chest radiography was recommended and preventive treatment was initiated if indicated. Of 27 visitors evaluated, four had positive TSTs (>5 mm induration; positive for an unknown duration) that were documented on initial screening. The TST induration measurements were 15 mm, 16 mm, 25 mm, and 6 mm, respectively. Since these visitors had no prior TST result documented, it is not known whether the current positive TST results represented prior infection or recent TST conversion, although past infection seemed most probable. All visitors with positive TSTs had normal chest radiographs. Preventive therapy was administered to two visitors.

Investigation of Health Care Workers

TSTs were performed on 260 health care workers with any NICU contact during the period in which the index case was present. All had prior negative TSTs on annual testing. TSTs were repeated 3 months after the initial TST. TST conversion occurred in two nurses (0.8%) who provided direct care to the index case. These two had positive TSTs (induration of 10 mm and 22 mm, respectively) documented on follow-up screening ~12 weeks after last exposure to the index case. Their initial TSTs showed no induration. The nurses had normal chest radiographs, and both received preventive therapy with isoniazid.

Investigation of the NICU Ventilation System

The survey of the NICU included review of the available floor diagrams and of the heating, ventilation, and air conditioning (HVAC) system. The 52-bed NICU is divided into 8 pods, each containing 6 beds per pod, and 4 isolation rooms. Approximately 50%–70% of the air is recirculated throughout the NICU, and the balance is supplied from outside air. Filters used in the HVAC system are >90% efficient in removing particles in the 1–5-µm range. The pods have an air-exchange rate of 17/hour. Air not recirculated is discharged through a stack located on the roof. This stack was built to be 25 feet from any potential air-intake sources.

The baby spent most of the time in an Air-Shields incubator (model C100; Air Shields, Hatboro, PA). This incubator is designed to isolate the infant from exposure to airborne particles; however, routine NICU procedures, such as physical examination or phlebotomy, bring the patient in contact with the ambient air and could result in transmission of tuberculosis from the infant to other people during these periods.

During the time the baby was placed on the oscillatory ventilator, secretions present in the tubing had the potential to be aerosolized into the pod when the tubing was removed from the baby’s airway. Air removed through suctioning is discharged to the outside through the central vacuum system. It is estimated that health care workers are exposed to an infant’s secretions for <10 seconds per episode of suctioning.

Discussion

Congenital tuberculosis infection can be acquired by aspiration or ingestion of infected amniotic fluid and by hematogenous spread. These routes of transmission often lead to primary involvement in the lung, gastrointestinal tract, liver, and bone marrow [3]. Hematogenous spread infects the fetus via the umbilical vein and primarily seeds the liver. Thus, a Ghon complex in the liver is considered diagnostic of hematogenous congenital transmission [3]. Amniotic fluid may become infected in utero by the spread of tuberculosis from endometrium to placenta. Alternatively, amniotic fluid may be contaminated by infected endometrium at the time of delivery, leading to perinatal infection of the baby via aspiration of amniotic fluid or infected decidua.

Symptoms in neonates are often nonspecific and can occur as early as 2–3 weeks of life [4]. Respiratory distress, fever, hepatosplenomegaly, and lymphadenopathy are most common [5]. Tuberculosis should be suspected especially when the mother has a history of tuberculosis, risk factors for the disease, or unexplained fever, pleurisy, night sweats, or premature labor [6]. Likewise, neonatal tuberculosis should be suspected if the baby has pneumonia unresponsive to antibiotics or unexplained symptoms of fever, respiratory distress, or organomegaly. Procedures that are most helpful for early diagnosis include early morning gastric aspirates, endotracheal aspirates, and lymph node biopsies. These specimens are most often smear- and culture-positive [5, 7].

Autopsy of our patient demonstrated severe pulmonary and mediastinal tuberculosis with miliary spread to other organs. This distribution of disease suggests infection via prenatal aspiration of contaminated amniotic fluid, either antepartum or intrapartum, rather than hematogenous acquisition.

In our investigation, the risk of exposure to tuberculosis via the respiratory route among other infants, visitors, and health care workers was considered low. In general, infants are poor transmitters of tuberculosis because they do not have a forceful cough. In the NICU setting, suctioning has a higher potential to generate infectious particles than does coughing. In this investigation, frequent suctioning of the index case in the last few days of life was most likely responsible for the TST conversion of one nurse. The other nurse with TST conversion
had frequent, direct contact with the index case throughout the 65 days of life.

Neonates <6 weeks old who are infected with *M. tuberculosis* do not react to TSTs because of their immature immune systems [8]. Skin test results, even in children <6 months of age, may not be reliable [9]. In this investigation, TSTs were performed on all exposed NICU babies, regardless of age. A positive TST would have confirmed that secondary transmission within the NICU had occurred. However, because negative TST results are unreliable in babies of this age, preventive therapy was recommended, irrespective of a negative skin test result. Moreover, preventive therapy must often be started for any child exposed to tuberculosis, even before a 3-month follow-up TST is performed, in order to reduce the risk of rapidly progressive disease in this age group.

In summary, congenital tuberculosis is a rare disease that is difficult to diagnose because of minimal or no symptoms in the mother and nonspecific symptoms in the infant. A high index of suspicion is required. In our case, the diagnosis of tuberculosis was not established until postmortem examination. Congenital transmission was confirmed by DNA restriction fragment analysis, which showed identical *M. tuberculosis* strains from the mother’s endometrial biopsy and the infant’s lung tissue. Secondary transmission of tuberculosis in the NICU setting is unusual, but it can occur.

In this investigation, TST conversion occurred in 0.8% of health care workers. Our experience underscores the importance of annual tuberculin skin testing of health care workers, establishing a baseline that is essential to the evaluation of subsequent transmission in a hospital. Empirical administration of isoniazid as preventive therapy to exposed neonates may be appropriate in the NICU setting. Follow-up of contacts was closely coordinated with the local health department. A systematic and rigorous approach to investigation of exposed infants, family members, visitors, and health care workers is essential.

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**References**