Objective. We describe the investigation of a tuberculosis (TB) exposure in which a neonatal intensive care unit (NICU) respiratory therapist was the index patient, as well as the rationale by which exposed infants were managed and possible explanations for the lack of transmission to these patients.

Design. Description of an exposure investigation.


Participants. Contacts of a respiratory therapist with pulmonary TB disease, including household members, healthcare coworkers, and infant patients.

Results. In addition to 5 household contacts, 248 healthcare coworkers and 180 infant patients were identified as possibly exposed during the 24 days that the index patient worked between December 3, 2004, and January 30, 2005. Tuberculin skin tests (TSTs) were performed for 233 of the 235 contacts with the greatest degree of exposure (household and coworker contacts) who had a previously documented negative TST result or whose TST status was unknown prior to the investigation. No cases of latent tuberculosis infection or TB disease were identified. Because of characteristics of the index case, the exposure duration and setting, the infants' small lung volumes, and lack of evidence of transmission to higher-risk contacts, infants were not clinically evaluated or empirically treated for TB disease. Surveillance for subsequent illness was carried out by primary healthcare providers and parents. No TB disease or unexplained illness in these infants was reported in the 20 months following the exposure.

Conclusion. After limited hospital exposure to a healthcare worker with pulmonary TB disease who is not highly contagious, neonates can be safely managed without specific evaluation for TB disease or empirical treatment.

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Although the incidence of tuberculosis (TB) disease in the United States is at a historical nadir,1 the goal of disease elimination makes the control of TB disease an issue of continued importance. Nosocomial TB exposures result not only from infected patients, but also from infected healthcare workers (HCWs), who account for 3.1% of the reported TB disease cases in the United States.1 Active TB disease in an HCW in a neonatal intensive care unit (NICU) can lead to relatively low-level exposure for a large number of patients who are at high risk of developing severe disease, should TB infection occur. We describe a recent case involving a NICU HCW with TB disease and the management of that individual's contacts.

Methods

Exposure Investigation

On January 25, 2005, a 49-year-old respiratory therapist who worked exclusively in the NICU was evaluated for a cough of 2-3 weeks duration. He reported recent flu-like symptoms, but denied fever, night sweats, and chills. He had no exposure to known or suspected cases of TB disease. His last tuberculin skin test (TST) for annual employment screening, performed in November 2003, was nonreactive.

A chest radiograph revealed a 1.2-cm nodule in the left mid-lung field and an irregular right apical opacity with adjacent pleural thickening (Figure 1). No cavitary lesions were

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Figure 1. Index patient’s chest radiograph from the day of presentation, January 25, 2005. Note the infiltrate in the apex of the right lung and small nodule in the left mid-lung field.

noted on this radiograph or by subsequent computed tomography. A TST was performed on February 1, and the HCW was placed on leave from work. At 72 hours, an induration 20 mm had developed at his TST site. Three sputum specimens were smear-negative for acid-fast bacilli. Staining of bronchoalveolar lavage fluid specimens, obtained the following week, was negative for acid-fast bacilli. The HCW was empirically treated with isoniazid, rifampin, pyrazinamide, and ethambutol. On February 22, cultures of 2 of 3 sputum samples and cultures of the bronchoalveolar lavage fluid specimen first grew acid-fast bacilli, which were identified as *Mycobacterium tuberculosis* complex strains by polymerase chain reaction on February 24. The isolates were susceptible to all antimicrobials tested. As the period of communicability may precede symptoms of TB disease,1 we estimated the onset of contagiousness as December 3, one month prior to symptom onset.

The index patient had 5 household contacts (all older than 13 years of age) who lived in the same dwelling during the infectious period and who were evaluated by the local health department. Work schedules for the index patient from December 3 through February 1 were cross-referenced with those of other HCWs to determine possible exposure. Working in the NICU on the same day as the index patient was deemed an exposure.

Computerized billing data that the index patient was required to generate for his services were used to determine patient exposure. In the main NICU, patient rooms are single occupancy, with 10%-20% air recirculation and 6.7 air exchanges per hour. A second NICU has 2 open ward–style rooms with approximately 5 beds per room. These rooms have 10%-20% air recirculation and approximately 10 air exchanges per hour. With the exception of a few negative-pressure isolation rooms, all rooms have neutral pressure relationships with the surrounding areas. Any patient who was in the second NICU on a day that the index patient provided services in the same room was considered exposed.

**Stratification of Exposures**

A “concentric-circles” approach was used to classify the risk of transmission of *M. tuberculosis* to contacts of the index case.2 Briefly, this approach places those at highest risk of contracting TB disease in the center circle of contacts. Those with the next lowest risk are placed in a circle surrounding the first, and so on, until a target-like diagram is constructed with the index case in the center (Figure 2). Placement of individuals in the concentric circle schema is based on several variables known to affect transmission of TB disease, including the duration and setting of exposure (specifically, volume and ventilatory exchanges of airspace) and individual contact characteristics. Evaluation of contacts begins with the center circle and proceeds outward, stopping where the rate of TST positivity falls to the expected baseline rate (eg, the baseline positive TST rate for HCWs in the institution).

The 5 household contacts were at highest risk and placed in the central circle because of their prolonged exposure to the index patient in their home and automobiles, which are relatively confined and poorly ventilated airspaces. The next circle contained those assigned an intermediate risk and included all exposed HCWs because of their frequent, but briefer, exposures in the well-ventilated hospital. The outermost circle contained those at lowest risk, the infant patients. The families of exposed patients were also placed in this same circle; however, family members were often not present during the brief exposures to the index case. Additionally, some patients were endotracheally intubated and only breathing air filtered by a ventilator circuit (Airlife Non-conductive Respiratory Therapy Filter [Cardinal Health], which has a bacterial filtration efficiency of 99.98%) during encounters. Also noteworthy in predicting risk to the patients was the very small respiratory minute volume (ie, volume of air breathed per minute, or “minute ventilation”) of a neonate, which predicts a much lower likelihood of inhaling TB droplet nuclei, compared with an adult.

TSTs were administered to all available HCWs except those with a previously documented positive result. A list of patient contacts was compiled, which included the names and addresses of their parents and their primary care providers. When it was determined that early evidence of transmission to higher-risk contacts was lacking, we recommended no TB disease evaluation or empirical drug therapy for lower-risk contacts. If TST conversions or TB disease linked to the exposure had been found subsequently, the need for evaluating and treating lower risk contacts would have been reconsidered.
RESULTS

The Index Patient

The index patient worked a total of 24 days during the estimated period of infectiousness. Directly observed therapy was administered by the local health department. The index patient returned to work after 3 weeks of therapy with isoniazid, rifampin, ethambutol, and pyrazinamide. No source for the index case was found after investigating for links to known TB disease cases in the hospital and in the community.

Household Contacts

No symptoms consistent with TB disease were found in household contacts. Four were judged to have had more than 96 hours of exposure per week, and 1 had 48 hours of exposure per week. None developed an induration after TSTs performed on 3 occasions (in February, May, and July 2005). All remained clinically healthy.

Healthcare Workers

A total of 248 HCWs were exposed. Nurses and nursing assistants accounted for 131 of these contacts. The others were physicians (n = 71) and individuals from environmental services (n = 21), respiratory therapy (n = 12), nutrition/dietary services (n = 5), radiology (n = 4), and clerical staff (n = 4).

Of these contacts, 18 had documented positive TST results prior to the exposure, did not have symptoms consistent with TB disease, and were asked to return to the Occupational Health Clinic if symptoms developed subsequently. Seven contacts no longer worked at the hospital and were unavailable for testing by the institution. Five that were located by the health department had nonreactive TSTs. Two contacts were not located. The remaining 223 HCWs had TSTs performed for baseline testing and again at 12 weeks or more after the last exposure. None had a positive TST result (defined as an induration with a diameter of 5 mm or greater). No cases of TB disease were identified in HCWs.

Patients

A total of 180 patients were investigated as contacts of the index case. The services performed by the index patient included maintaining respiratory apparatus or pulse oximeters, obtaining blood gas analysis specimens, chest physiotherapy, and administration of inhaled therapy.

Twenty-two exposed patients were hospitalized at the beginning of the investigation, and 12 had died. Their families were informed of the exposure directly by a neonatologist. None of these patients were judged to have clinical illness, chest radiograph findings, or autopsy findings consistent with TB disease. For patients who had been discharged from the hospital (n = 146), their primary care provider was notified by both telephone and mail. After primary care providers were notified, each family was notified similarly. In all, 144 (80%) of the 180 families were contacted in person or by telephone. Addresses were available for all patients who were not currently hospitalized. Seven (4.8%) of 146 letters sent were returned as undeliverable. Because of the index case’s sputum smear status, chest radiograph findings, and his...
families' negative TST results, no evaluation for TB disease was recommended for the patients. Primary care providers and families were asked to report subsequent illnesses that raised concerns about TB disease to the institution. The notification of primary care providers and families was well received. Both groups expressed gratitude for the caution and transparency with which the investigation was conducted.

When final evaluations found no transmission of *M. tuberculosis* to higher risk contacts, the patients' families and primary care providers were informed by mail and reminded to report illnesses suspected of being TB disease. Twelve (7.1%) of 168 follow-up letters sent to families were returned as undeliverable. Only 4 (2.2%) of 180 families could not be reached at least once. No associated cases of TB disease, latent TB infection, or unexplained illness in contacts were reported in the subsequent 20 months.

**Discussion**

The results of this investigation are consistent with other reports which have shown that transmission of *M. tuberculosis* to hospitalized neonates was not identified or was rare after exposure to an adult with pulmonary TB disease. The likely reason for the rarity of transmission to neonates exposed in the hospital is not known, but presumably it is multifactorial. Characteristics of the index case and the environment in which exposure occurs are clearly important. Cavitary disease and smear-positive sputum are 2 characteristics proven to increase *M. tuberculosis* transmission. 

However, other reports of nursery exposures noted that the index patients possessed one or both of these factors without frequent transmission to neonate patients. Moreover, our index patient lacked both factors. The hospital setting affords active ventilation, larger air volumes, and often only brief duration of exposure to a HCW with undiagnosed TB disease. All of these factors have been shown to predict lower transmission risk, and Centers for Disease Control and Prevention guidelines advocate using such factors to prioritize contacts for clinical evaluation.

Infants clearly have a higher risk of developing TB disease, including disseminated disease, once infected. Presumably, the higher risk of developing TB disease should decrease the threshold for initiating evaluation. It has been suggested that infants are more likely than older persons to become infected after exposure to *M. tuberculosis*, but this hypothesis appears to be based on the putative role of immature alveolar macrophage defenses, rather than clinical data.

A biologically plausible counterargument can be made that infants are less likely to be infected than older people. The risk of inhaling an infectious dose of *M. tuberculosis* is related not only to the air density of droplet nuclei, but also to the alveolar respiratory minute volume of the patient. The estimated respiratory minute volume of our patients (most of whom weighed less than 2 kg) was 250-500 mL, compared to 6,000 mL in an average adult. Available clinical data come from studies of household exposures to TB disease in which rates of infection in infants and young children have been shown to be similar or significantly lower, compared with older children and adults after exposure to *M. tuberculosis*. This might be due to a lower sensitivity of TSTs in infants and higher rates of exposure to TB disease outside the home for older contacts; however, these data do not support the notion that exposed infants are more likely to be infected than adults.

If neonates are not more (and are conceivably less) likely than adults to become infected with *M. tuberculosis* given a similar exposure, the crucial issue is determining what constitutes an exposure sufficient to warrant specific diagnostic evaluation. A lower risk of contagiousness in our index patient was predicted by negative sputum smear results and the lack of cavitary disease. In addition, after using a “concentric-circles” approach to stratify risk to contacts, we were most reassured by the lack of transmission to persons with a greater degree of exposure and larger respiratory minute volume. Because TST results cannot reliably be used to rule out TB infection in neonates (especially premature infants, for whom there are no data on TST validity), empirical treatment with isoniazid is recommended for infants with an *M. tuberculosis* exposure. Although isoniazid is generally well tolerated by infants, we opted against taking the risk of treating 168 neonates, most of whom were premature and had multiple medical problems. This decision was based on the successful experience of others who did not treat in similar situations (and personal communication, Jeffrey R. Starke, MD, February 2005) and our estimation that our patients were at exceedingly low risk of acquiring TB disease or infection from their exposure.

Recently published Centers for Disease Control and Prevention documents provide a thorough overview of TB disease control and contact investigation in both community and healthcare settings. However, the guidelines do not take into account the nuances of exposure in specialized settings, such as a NICU. Given the vulnerability of this patient population to developing TB disease, the potential for more than 1,000 infants to be affected by a single case, and the generally low level of exposure that occurs in a NICU, specialized guidelines to standardize management of infants exposed to *M. tuberculosis* in the healthcare setting may be warranted.

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