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Congenital Tuberculosis

A New Concern in the Neonatal Intensive Care Unit

Desi M. Newberry, DNP, NNP-BC; Tracey Robertson Bell, DNP, NNP-BC

ABSTRACT

Background: Congenital tuberculosis (TB) is rare in the United States. Recent immigration patterns to the United States have made the diagnosis of congenital TB an important public health issue.

Purpose: To explore the epidemiology, pathophysiology, diagnostic evaluation, treatment, and prognosis for congenital TB. The implications for exposed healthcare professionals in the neonatal intensive care unit (NICU) setting are also explored.

Methods/Search Strategy: Relevant articles were accessed via PubMed, CINAHL, and Google Scholar.

Findings/Results: Until 1994, fewer than 400 cases of confirmed congenital TB had been reported in the literature worldwide. An additional 18 cases were reported from 2001 to 2005. Neonatal providers need to be aware of the potential for congenital TB infection as the immigrant population in the United States continues to increase, many of whom originate from TB endemic countries.

Implications for Practice: The interpretation of TB-specific tests is problematic in newborns due to decreased sensitivity and specificity. Congenital TB should be ruled out in infants with signs and symptoms of sepsis or pneumonia and in whom broad-spectrum antibiotic therapy does not improve their clinical status.

Implications for Research: The interpretation of TB-specific tests is problematic in newborns due to decreased sensitivity and specificity; more research is needed regarding best practice in diagnosis. Established protocols are needed to address the healthcare of TB-exposed providers in the NICU.

Key Words: congenital tuberculosis, genital tuberculosis, *Mycobacterium tuberculosis*, neonatal intensive care unit, pulmonary tuberculosis, tuberculosis

Congenital tuberculosis (TB) is rare in the United States, with only an estimated 300 to 400 reported cases in the literature. While the actual incidence of congenital TB transmission has not been reported, the number of cases is likely underreported because of nonspecific symptoms in the infant, which are often misdiagnosed as other infections.[1] Infants with congenital TB are at a higher risk for pneumonia and respiratory distress. The mortality rate for congenital TB is 40% to 100%, with higher mortality associated with delayed or lack of appropriate treatment.[1]

Overall, TB rates in the United States are decreasing; an exception is in pregnant women and in non–US-born persons.[2] Recent immigration patterns to the United States have made the diagnosis of congenital TB an important public health issue. As a result, clinicians must be cognizant of the possibility of congenital TB in the United States and the implications of caring for these infants.[1] Congenital TB should be included in the differential diagnosis in the case of an infant who fails to respond to traditional antibiotic and supportive therapies in the neonatal intensive care unit (NICU), especially if born to a mother with risk factors. The purpose of this article is to explore the epidemiology, pathophysiology, diagnostic evaluation, treatment, and prognosis for congenital TB. The implications for exposed healthcare professionals in the NICU setting are also explored.

EPIDEMIOLOGY

TB remains a global health crisis, with as much as one-third of the world's population infected.[3,4] In 2016, there were an estimated 10.4 million new cases of TB and 1.8 million mortalities resulted from the infection.[2,5] Most of the world's cases of TB originate in Southeast Asia (61%), whereas the highest incidence occurs in southern Africa (26%).[3] Of the more than 10 million newly identified cases of TB in 2016, India, China, Indonesia, the Philippines, Pakistan, Nigeria, and South Africa made up 64% of the total cases.[5] Of those 10.4 million newly infected people, 3.2 million were women.[5]

From 2014 to 2015, the foreign-born population in the United States increased by 2%.[6] In 2015, it

Author Affiliations: *WakeMed Health and Hospitals, Raleigh, North Carolina (Dr Newberry); East Carolina University, Greenville, North Carolina (Drs Newberry and Robertson Bell); and Emory University, Atlanta, Georgia (Dr Robertson Bell).*

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Correspondence: *Desi M. Newberry, DNP, NNP-BC, 5917 Larboard Dr, Apex, NC 27539 (newberryd14@ecu.edu).*

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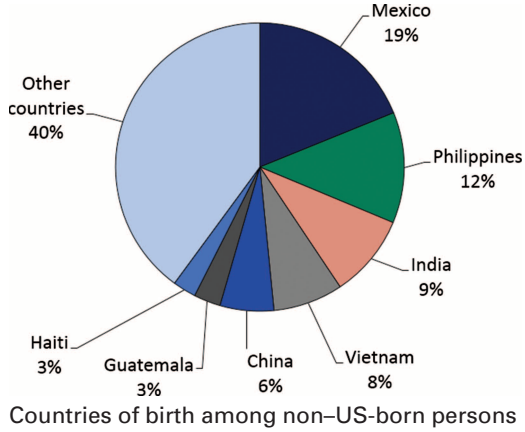
was estimated that 43.3 million people (13.5%) of the US population were immigrants; 51% were women.[6] Of the TB cases occurring in the United States, 66% occurred in persons who were born outside the United States.[7] The rate of TB infection is 13 times higher for foreign-born persons when compared with persons born in the United States, with the majority of the cases occurring in those who have been in the United States for more than 5 years.[7] In the United States, more than 60% of adults and more than 25% of children with TB are foreign-born.[3] The top 5 countries of origin for foreign-born cases in the United States are Mexico (18.9%), the Philippines (12.6%), India (9.4%), Vietnam (7.9%), and China (6.1%) (Figure 1).[2]

Worldwide, the TB mortality rate decreased by 37% between the years of 2000 and 2016.[5] In the United States, the overall TB mortality rate is 1.9 per 100,000 cases and the incidence of TB decreased by 1.5% from 2014 to 2015.[5] In addition, 2016 marked the lowest TB rate in US history, with 9272 cases or 2.9 per 100,000 persons.[2] This describes a 3.6% decrease from 2015.[2] TB rates are highest in urban and low-income areas.[3] California, Texas, New York, and Florida have the highest TB rates in the country.[7]

Pregnant Cases

Despite an overall decline in TB rates in the United States, the rate of TB during pregnancy is increasing.[8] In a retrospective cohort study, El-Messidi et al[8] found an overall incidence of TB (in the United States) of 26.6 per 100,000 births, with an increasing trend from 1.92 to 4.06 per 10,000 births in the 9-year study period ($P < .0001$). The incidence of TB during pregnancy was higher in women who were 25 to 34 years of age, Hispanic, lower-income, and a Medicaid recipient and those who received treatment in an urban teaching hospital.[8] It has been estimated that the risk of vertical transmission from the TB-infected mother to the fetus could be as high as 16%.[9]

FIGURE 1



Countries of birth among non–US-born persons reported with tuberculosis, United States, 2016.

Congenital Cases

Most of the information on congenital TB comes from cases studies. Until 1994, fewer than 400 cases of confirmed congenial TB had been reported in the literature worldwide.[1,9] An additional 18 cases were reported from 2001 to 2005.[10]

A more recent case was described in North Carolina in which a 25 weeks' gestation infant was admitted to the NICU with respiratory distress and fever.[11] The infant died at 17 days of life; a diagnosis of congenital TB was made postmortem. Unbeknownst to the healthcare team, the mother of the infant had presented to an infertility center 2 years prior and genitourinary TB was diagnosed at that time.

Genital TB

Genital TB is a form of extrapulmonary TB. Cases of congenital TB are noted in the literature with mothers who have conceived via in vitro fertilization secondary to infertility.[8] In these situations, the mothers were not screened for TB but the etiology of their infertility was related to TB; subsequently, they became pregnant and thus passed the TB to their fetuses during pregnancy. TB testing is not standard with fertility treatment, and the Food and Drug Administration (FDA) does not mandate TB testing of human cells.[12,13]

Cases of genital TB are uncommon in the United States; however, the incidence is as high as 3% to 17% of infertility cases in endemic countries.[14] India is an example where genital TB is the etiology for 40% of tubal damage.[14] Gleeson et al[15] described the case of an Irish healthcare worker with previous TB exposure but negative tuberculin skin test (TST) who delivered an infant with congenital TB, highlighting the importance of TB testing in healthcare workers with gynecological complaints. It is important for healthcare workers to be aware of the potential sequelae of genital TB in regard to fertility and consider the elevated risk for a mother with a history of infertility, especially with the rising immigrant population from TB endemic countries.

PATHOPHYSIOLOGY

Mycobacterium tuberculosis (Mtb) is the most virulent human pathogen of the *Mycobacterium* genus and is the bacterium responsible for TB infection.[3] Mycobacteria are nonmotile, non–spore-forming, weakly gram-positive rods. Mycobacteria are also acid-fast. Other species of the *Mycobacterium* genus include *M africanum*, which is rare in the United States, and *M bovis*, which causes a similar spectrum of illness as Mtb but with different epidemiology, treatment, and prevention.

Epidemiologic Stages of TB

The mode of TB transmission is respiratory. The epidemiologic stages of TB include exposure, infection, latency, and disease. Exposure occurs with close contact of a cough droplet in an untreated individual. Adults are more likely than infants and young children to spread TB due to larger pulmonary cavities and a more forceful cough. The TB microdroplets hang in the air and are breathed in by the exposed. The droplet nuclei of TB can remain suspended in the air for several hours. Transmission is more likely to occur in poorly ventilated and enclosed areas.

Approximately 35% of exposed adults will become infected with TB.[5] A positive TST or interferon-γ release assay (IGRA) is consistent with TB infection. Most people who are infected with TB are able to fight the bacteria and develop latent TB.

Individuals with latent TB do not have symptoms and cannot spread TB to others. Latent TB may progress on to active TB disease if left untreated. Those with immune compromise, poor nutrition, smoking, alcoholism, and older age are more likely to progress on to active TB disease.[3]

Of adults infected with Mtb, 90% will not develop TB disease; the remaining 10% will most likely develop pulmonary TB.[3] Fifty percent of those who develop active TB disease will do so within 2 years of exposure. Later reactivation can also occur.

Innate Immunity

There are 3 stages of innate immunity to protect exposed individuals from progressing to TB infection or disease: first-line innate responses, adaptive immunity, and the formation of a granuloma. A rapid response occurs when Mtb is inhaled into the distal airways and taken up by alveolar macrophages. These macrophages perform first-line innate immunity; they recognize TB. An inflammatory response next occurs through pathogen recognition receptors. The inflammation, in turn, recruits other immune cells, including neutrophils and Natural Killer (NK) cells. The NK cells produce interferon-γ; this further activates macrophages to increase bacterial control. Autophagy also occurs with envelopment of Mtb.[5]

During adaptive immunity, death of macrophages occurs, releasing Mtb. The Mtb is taken up by additional macrophages and dendritic cells. The dendritic cells then migrate to the lymph nodes where T cells are activated. In addition, CD4 cells migrate to the lungs and activate macrophages to control the TB. Finally, a granuloma forms at the disease site, playing a primary role in the isolation of Mtb. TB disease can occur with breakdown of this granuloma.[3]

Of note, a live attenuated strain of *M bovis* is utilized in the bacille Calmette–Guerin (BCG) vaccine. The BCG vaccine is one of the most common vaccines used worldwide but not generally in the United States. The BCG vaccine can be given to infants who will be continually exposed to an untreated or ineffectively treated adult. The BCG vaccine does not completely prevent active TB but rather decreases the risk for disseminated TB, including meningitis. The BCG vaccine should not be given to pregnant women.[16]

The epidemiologic stages of TB are essentially the same during pregnancy, with the inclusion of the genital tract as a source of direct dissemination to the fetus. The fallopian tubes are most commonly affected (90%) in genital TB, with the uterus, ovaries, and cervix identified less commonly.[3] Mycobacteria can also cause acute chorioamnionitis.

Congenital TB

Congenital TB is transmitted in utero through the umbilical vein, perinatally via ingestion or aspiration of infected amniotic fluid, or through direct contact with maternal genital lesions.[1,17-19] Of the aforementioned, the usual mode is through an infected placenta, through the umbilical vein, to the fetal liver or lungs.[14] In the newborn, the pathogenesis is dependent on the route of transmission; transmission via the umbilical vein results in primary liver disease, potentially followed by lung, bone marrow, bone, adrenal, kidney, gastrointestinal, spleen, skin, and lymph node involvement. Aerosolized transmission after birth from a contact will result in pulmonary disease and is not considered congenital TB.[3]

Infants and children have a 5- to 10-fold increased risk for the development of TB disease after infection in comparison with adults. In addition, because of immaturity of macrophages, dendritic cells, and T cells, infants have an increased risk of disseminated disease, including meningitis and miliary disease.

SYMPTOMS

The diagnosis of congenital TB is often challenging in newborns because many of the markers are nonspecific to TB and markers specific to TB have poor sensitivity in newborns.[10,12,20] Oftentimes, maternal history, maternal diagnosis after delivery, and/or clinical symptoms are the only basis for diagnosis of congenital TB.[20] In fact, clinical criteria remain the gold standard in diagnosis.[18] This is especially important because as many as half of mothers are undiagnosed at the time of their infant diagnosis.[21]

Congenital TB symptoms may present at birth but more commonly present in the first 2 to 4 weeks of life.[1,5,17,18] The onset of symptoms in infants tends be quicker than in older children and adults.[17] Clinical manifestations of congenital TB can be varied, nonspecific, and difficult to differentiate from neonatal bacterial or viral sepsis (Table 1).[1,17,18,22] The sickest

TABLE 1. Congenital Tuberculosis Symptoms	
Nonspecific[1,5,17,18]	Fever Respiratory distress Pallor Lymphadenopathy Jaundice Hepatosplenomegaly
Respiratory[1,17,18]	Tachypnea Apnea Cyanosis Cough Rales wheezing
Neurologic[1,5,17,18]	Lethargy Irritability Meningitis Seizures
Gastrointestinal[1,17,18]	Poor feeding Failure to thrive Abdominal distention Vomiting
Other[1,5,17,18]	Rash Ear discharge Otorrhea/mastoiditis Facial paralysis Bone deformity
Rare[1]	Hemophagocytic syndrome

infants may develop respiratory failure, shock, disseminated intravascular coagulation, and multiple organ failure.[1,17]

DIAGNOSIS

Congenital TB should be ruled out in infants with signs and symptoms of sepsis or pneumonia and in whom broad-spectrum antibiotic therapy does not improve their clinical status.[1,5,17,18] Peng et al[1] suggest that congenital TB should be considered early on in infants with respiratory distress, hepatosplenomegaly, and fever in the first 3 months of life, no improvement after antibiotic therapy, when other congenital viral infections are ruled out, and with a positive history of maternal TB during the pregnancy. Other criteria worthy of consideration include a high lymphocyte count in the cerebrospinal fluid (CSF) and abdominal distention with ascites and hepatomegaly.[17]

Historically, diagnostic criteria for congenital TB consisted of the demonstration of a primary hepatic complex, which requires an open surgical procedure or autopsy, to confirm liver and regional lymph node involvement. In 1994, Cantwell et al[21] proposed revised diagnostic criteria for congenital TB. The infant must have proven tuberculous lesions and at least one of the following: (1) lesions in the first week of life; (2) a primary hepatic complex or caseating hepatic granulomas; (3) tuberculous infection of the placenta or the maternal genital tract; or (4) exclusion of the possibility of postnatal transmission by a thorough investigation of contacts.[21] A primary complex is the typical lesions of primary TB; caseation is diseased tuberculin tissue that is necrotic and cheese-like in appearance. The presence of a hepatic granuloma is most consistent with congenital TB versus postnatal transmission and can help differentiate the timing of infection acquisition.[17]

TB-Specific Tests

The interpretation of TB-specific tests is problematic in newborns due to decreased sensitivity and specificity. TB-specific tests include the TST, IGRA, acid-fast bacilli (AFB) smear, culture, microscopic observed drug susceptibility (MODS) testing, nucleic acid amplification tests (NAATs), and histologic examination.

Tuberculin Skin Test

The TST consists of an intradermal injection of Mtb membrane proteins; the injection site is then monitored for skin induration. The typical skin induration of a positive result is caused by the influx of *Mycobacterium*-specific CD4 cells.[3]

The TST is universally negative in newborns.[1,17,18] Therefore, infants younger than 3 months will have a false-negative result. The TST generally gives positive result after several months.[18]

The specificity of the TST is reduced by the BCG vaccination, especially in infants.[22] Other disadvantages of the TST include low sensitivity in cases of active TB, malnutrition, coinfection with parasites, and immunodeficiency.[23] Of these, malnutrition and immunodeficiency pertain to infants in the NICU.

Interferon-γ Release Assays

IGRAs measure the individual cell-mediated response to determine the likelihood of Mtb infection. Blood cells are exposed to Mtb-specific antigens, which are then taken up by macrophages and dendritic cells; these, in turn, are then presented to Mtb-specific T cells, which produce interferon-γ.[3] The antigens in IGRAs are present in both Mtb and *M bovis*; a benefit in older children is that the IGRA results are not affected by administration of the BCG vaccination.[3,23] FDA-approved IGRAs include the QFT Gold In-Tube and T-Spot TB test.

The Centers for Disease Control and Prevention and the American Academy of Pediatrics (AAP) recommend testing with IGRAs in the case of BCG vaccination and in those unlikely to return for TST reading.[23] Furthermore, the AAP lists IGRAs as acceptable in children younger than 5 years; in fact, IGRAs have been found to be effective in children younger than 6 months.[23] However, the IGRA is almost always negative in newborns due to

immature T-lymphocyte activity.[1,17,18,24,25] Therefore, the AAP does not recommend use of IGRAs in children younger than 2 years unless TB disease is suspected.[3] Neither the TST or IGRA differentiate Mtb infection from active disease.[22] Both tests take 2 to 10 weeks to turn positive after exposure.[3]

AFB Smear

The detection of AFB in smears offers the first evidence of mycobacteria; however, the AFB is not specific to Mtb (Figure 2). AFB results are available within 24 hours. However, AFB results provide a preliminary, presumptive diagnosis for TB but cannot distinguish from other mycobacteria in stained specimens. As such, AFB results must be confirmed with culture.[23]

Cultures

Cultures specific for Mtb can be obtained from the blood, CSF, endotracheal or bronchial aspirate, gastric aspirate, urine, stool, ear swab, and biopsy specimens of lymph nodes, liver, and skin.[17,20] Of these specimens, serial gastric aspirates appear to be the most useful in infants.[3] Cultures from the more invasive bronchoalveolar lavage have not proven to be any more sensitive than gastric aspirates in children.[18] In addition, the usefulness of sputum cultures is limited because of the inability to obtain expectorate samples from neonates.[22] Pleural fluid can be cultured in cases with pleural effusions, and CSF in cases with suspected meningitis.[3]

Direct visualization of Mtb through microscopy results in less than 5% sensitivity, most likely due to lower bacterial loads in infants.[3] It appears difficult to isolate mycobacteria in infant samples with low mycobacterial yields, with negative smears and polymerase chain reaction (PCR) detection in as many as 30% of neonatal cases.[17,18,26] Both microbiologic studies for detection of Mtb bacilli and Mtb growth have shown poor sensitivity in young children, as low as 40%.[5,22] Another limitation is that Mtb grows very slowly in culture and longer time-to-positive results frequently occur in children because of decreased bacterial loads.[3] However, infants do have a higher bacillary load than older children due to more progressive dissemination of the disease.[18]

Microscopic Observed Drug Susceptibility

In MODS, the culture and sensitivity are performed simultaneously. Results are available in as quick as 7 days. One such test, the rapid test Xpert MTB/RIF®, can also detect resistance to rifampin (RIF).[3]

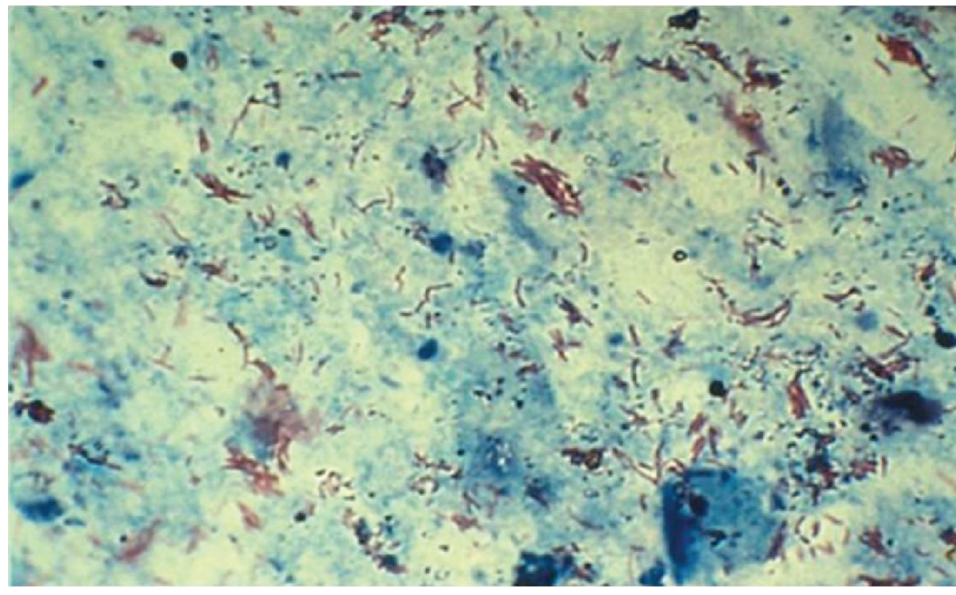
Nucleic Acid Amplification Tests

Other tests are available for the detection of DNA specific to Mtb.[22] PCR offers a fast and inexpensive technique used to copy small segments of DNA. This amplification aids in the detection of low-density bacteria. A recent Cochrane review found 88% sensitivity and 98% specificity with DNA amplification techniques.[3] The use of NAATs in the United States is limited because of cost, availability, and lack of demand from healthcare providers.[27]

Histology/Pathology

Histologic examination of the liver, placenta, lymph nodes, or other affected organ can be helpful in

FIGURE 2



AFB Smear. AFB indicates acid-fast bacilli.

diagnosis.[3] Biopsy can be utilized to demonstrate the presence of granulomas. Any caseating of hepatic granulomas or evidence of tuberculin infection of the placental is diagnostic.[1]

Nonspecific Markers

Nonspecific tests include complete blood cell counts, C-reactive protein, and radiographic tests. Nonspecific markers found in congenital TB include neutrophilia, thrombocytopenia, and elevated C-reactive protein.[1] The activation of neutrophils is theorized to secrete chemokines and cytokines and actively limit mycobacterial growth.[28] A low neutrophil count is concerning for and is associated with a bad prognosis.[1] Imaging studies such as radiography, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) can be helpful to identify anatomical lesions associated with TB disease.[22]

Radiologic Evaluation

Initial chest radiographs may have normal findings, with abnormal findings appearing by 4 to 8 weeks' postnatal age.[1,17] Supine and lateral views can be diagnostic.[22] Abnormal chest x-ray findings may be nonspecific and include miliary TB (seeding of Mtb in the lung), multiple pulmonary nodules, cystic lesions, lobar, bronchial, or interstitial pneumonia, mediastinal adenopathy, lobar opacification, large airway compression, lung primary complex, pleural effusion, or pleuritis.[1,5,17,22] Abdominal radiographs may show normal to multiple focal lesions in the liver and spleen, with liver primary complex, hepatosplenomegaly, or ascites.[1,3]

Pleural or pericardial effusions can be confirmed via ultrasonography.[22] Abdominal ultrasonography can show hypoechogenic foci in the liver or spleen, ascites, and lymphadenopathy.[5,17,22] CT and MRI are not used frequently due to risks associated with high radiation exposure, expense, and inaccessibility in low-resource areas but may be useful in unconfirmed or complicated cases.[22]

MANAGEMENT

Early recognition and treatment of congenital TB are crucial. The treatment regimens for congenital TB and postnatally acquired TB are identical.[5] Adherence to the recommended combinations and dosages is imperative to decrease drug resistance.[23] Special considerations in the recommended treatment regimens exist in cases of disseminated disease, meningitis, and in breastfed infants. In addition, the AAP offers recommendations for mother–infant dyads during the birth hospitalization.[23]

The first-line multidrug treatment regimen for congenital TB consists of oral INH, RIF, and pyrazinamide (PZA) for the first 2 months.[5,23] An aminoglycoside is added to the treatment regimen in cases of disseminated disease.[5,23] An additional regimen of 4 months of INH and RIF is indicated after the initial 2 months of treatment.[3,23] For infants with TB meningitis, it is prudent to consider the inclusion of corticosteroids to the drug regimen to minimize neurologic sequelae.[3,13] Exclusively breastfed infants should also be supplemented with pyridoxine, as INH is a pyridoxine metabolism inhibitor, leading to increased potential for seizures or peripheral neuritis.[5,23,29] See Table 2 for first-line drug information.

Second-line drugs include ethionamide, fluoroquinolones, and streptomycin and are rarely used in congenital TB because of decreased effectiveness and increased risk for toxicity.[23] The fluoroquinones are not FDA-approved in children younger than 18 years.[23] These second-line drugs should only be used in consultation with a pediatric infectious disease specialist.

Drug susceptibility testing should be performed on the neonate or the case patient.[3] In addition, microbiologic testing of the placenta offers an additional means to aid in identification of the TB strain.[3] An extended course of multidrug therapy is recommended as a means to reduce the incidence of bacterial resistance.[30] TB drug resistance has remained stable for the past 20 years,[7] and young children are at a low risk for the development of resistant TB.[22] The most common form of resistance is INH monoresistance (8.7% of cases with susceptibility results).[7] In the United States in 2015, only 0.4% and 1.2% of confirmed TB cases were multidrug resistant for US- and foreign-born cases, respectively.[2] There was only 1 case of extensively drug-resistant TB in 2016 (resistance to INH, RIF, fluoroquinolones, and at least one of 3 of the second-line TB drugs).[7]

The AAP recommends that the infant and the mother can room-in together in the case of an mother of baby with a positive TST or IGRA but negative chest x-ray findings. No treatment is indicated for the infant. The source patient should be treated in the case of latent TB.[23]

Infants of mothers with symptoms, abnormal chest radiographs, and confirmed TB disease should be evaluated and treated. If the evaluation is negative, the infant is treated with INH and pyridoxine. A TST should be performed at 3 to 4 months. A positive TST requires reassessment for TB disease. If TB disease is ruled out with a positive TST, continuation of INH for a total of 9 months with monthly follow-up is required. Alternatively, the INH can be discontinued if the TST is negative at 3 to 4 months, provided the source case is compliant with therapy and has a good response to treatment.[3,23]

In addition, the mother and the infant should be separated until the infant's evaluation is complete, treatment is initiated, and the source patient is compliant with treatment.[23] Breastfeeding is recommended once these criteria are met; first-line TB drugs cross into human milk in small amounts but have not been

TABLE 2. First-Line Drugs in the Treatment of Congenital Tuberculosis

	Mechanism of Action	Available Routes	Special Considerations	Adverse Reactions
Isoniazid (INH)	Bactericidal, inhibits synthesis of mycolic acids—a component of the bacterial cell wall[29]	PO, IM	Pyridoxine supplementation recommended	Seizure, rash, gynecomastia, hyperglycemia, metabolic acidosis, pyridoxine deficiency, nausea, vomiting, bilirubinuria, anemia, eosinophila, lymphadenopathy, thrombocytopenia, hepatitis, hyperbilirubinemia, increased serum transaminases, optic atrophy, optic neuritis, fever[29]
Rifampin (RIF)	Bactericidal, inhibits bacterial RNA synthesis[29]	PO, IV	Excreted in bile and urine—patients will have orange urine, sweat, and tears[23]	Edema, flushing, ataxia, confusion, dizziness, numbness, psychosis, pruritus, urticaria, adrenocortical insufficiency, increased uric acid, hematuria, decreased hemoglobin, disseminated intravascular coagulation, hemolytic anemia, leukopenia, thrombocytopenia, jaundice, osteomalacia, conjunctivitis, acute renal failure, increased blood urea nitrogen, flu-like symptoms, fever[29]
Pyrazinamide (PZA)	Bacteriostatic or bactericidal depending on concentration at infection site, lowers the pH of *Mycobacterium* environment, exact mechanism not known[29]	PO	May increase levels and effects of RIF[29]	Malaise, anorexia, nausea, vomiting, arthralgia, myalgia[29]

Abbreviations: IM, intramuscular; IV, intravenous; PO, orally.
An aminoglycoside is added in cases of disseminated disease. A corticosteroid may be added in cases of meningitis.[23]

linked to any adverse effects in the infant.[29] Some second-line drugs are contraindicated.[3]

The infant will require frequent appointments with a primary care provider to ensure compliance with the regimen as well as monitoring for side effects from the drug therapy.[13] To prevent drug resistance and ensure adequate treatment, the family will need to strictly adhere to the treatment regimen. Compliance may be improved with once-daily dosing.[30] Adverse reactions are not common in children with first-line TB drugs.[22] Hepatic dysfunction can be common with this category of drugs, so the infant will also require monthly evaluation of liver functions as well as education and counseling for the family regarding the signs and symptoms of liver failure.[30] Finally, an infant with confirmed congenital TB will need HIV testing, as there is a high rate of coinfection with HIV and TB.[23,30]

IMPLICATIONS FOR HEALTHCARE PROVIDERS

In addition to the medical management of the infant, the provider needs to be aware of the potential risk to the healthcare professionals involved in the care of this infant. The healthcare workers who have close contact to the infant and those involved in respiratory suctioning are at an increased risk for transmission.[31,32] Infants have less risk for transmission of TB due to typically weak coughs.[31] Furthermore, the risk for transmission of TB in young children is typically low due to the relatively low bacilli load, but the risk can be higher with congenital TB, as the concentration of tuberculin bacilli is higher in the sputum.[33]

Mouchet et al[33] describe the case of a 29-week gestation male neonate, diagnosed with congenital TB on day of life 102. In this postexposure investigation, all nursery and obstetric staff members, as well as employees who had been in contact with the nursery during the time frame the infant was hospitalized, were evaluated. The evaluation process consisted of chest radiographs or TSTs, completed by occupational health.[33] The most significant risk factor for the healthcare providers was extended contact with the infected infant (in this study, the infant's primary physicians and nurses). Nineteen percent (6/32) of the primary caregivers received treatment

Summary of Recommendations for Practice and Research	
What we know:	• Congenital TB is rare. • Recent immigration patterns in the United States have made congenital TB an important public health issue. • The mortality rate for congenital TB is 40% to 100%. • The interpretation of TB-specific tests is problematic in newborns due to decreased sensitivity and specificity
What needs to be studied:	• Creation of best practice protocols on the diagnostic workup for congenital TB in the NICU. • Creation of best practice protocols on management of postexposure healthcare providers in the NICU. • Determination of transmission risks for TB-exposed providers, other infants in the nursery, and their families.
What we can do today:	• Neonatal providers need to be aware of the potential for congenital TB infection as the immigrant population in the United States continues to increase, many of whom originate from TB endemic countries • Congenital TB should be ruled out in infants with signs and symptoms of sepsis or pneumonia and in whom broad-spectrum antibiotic therapy does not improve their clinical status. • Recognize the symptoms of congenital TB early and establish prompt treatment to improve prognosis.

for TST conversions. The overall transmission rate was 4.3% among the 139 healthcare workers screened. This rate was compared with the 2 previous annual positive TST rates of 1.3% ($P = .0374$) and 2.3% ($P = .2391$) in the same institution. For any employee with a positive skin test but negative chest x-ray findings, INH was prescribed. If the contact with the infant was less than 3 months before screening and the employee had negative results, a second screening was recommended.[33]

A more recent congenital TB exposure in a North Carolina NICU is thought to have resulted in newly positive TSTs in 7 healthcare providers (7/135; 5%) and 1 visitor (1/23; 4%).[11] Of the 7 providers, all had performed either intubation or open suctioning on the case patient, most likely resulting in aerosol generation. Twenty-six NICU infants were considered exposed; these infants were screened by TST, IGRA, and/or chest radiographs. All screens were negative; however, the North Carolina Department of Public Health recommended preemptive treatment with INH for 9 months due to the concern for false-negatives in infants.[11]

PROGNOSIS

Prognosis is dependent on the severity of disease, drug resistance patterns, and patient adherence to treatment.[3] TB in pregnancy results in a higher incidence of early fetal demise, preeclampsia, antepartum hemorrhage, and subsequent infertility.[3] Infants born to mothers with untreated, active TB disease are more likely to have intrauterine growth restriction, low birth weight, and low Apgar scores.[3]

There is a paucity of data on neonatal outcomes. However, infants who presented with symptoms before day of life 21, white blood cell count more than 12×10^9, low leukocyte count, and intracranial granulomas had poorer prognostic outcomes.[1,3] In a review of 170 cases of confirmed congenital TB (utilizing Cantwell's criteria), Peng et al[1] found that confounding factors of prematurity, liver dysfunction, or thrombocytopenia did not affect the mortality rate. In those patients, the mortality rate decreased from 100% to 21.7% with a multidrug regimen that included INH and RIF.[1]

The overall mortality for infants with congenital TB is 100% if undiagnosed, 40% to 50% if diagnosed late, and 20% if diagnosed early and adequately treated.[1,14] Delayed infant diagnosis carries a 5-fold higher mortality rate in comparison with prompt diagnosis and treatment.[15]

CONCLUSION

Congenital TB is a rare neonatal disease. Diagnosis of congenital TB in the neonate can be difficult, as many of the symptoms are nonspecific and associated with other more common neonatal disease processes. Prompt and early diagnosis is associated with improved outcomes. The healthcare provider must also understand the risks associated with potential exposure to TB in the nursery/NICU setting and the need for testing and possible treatment. The possibility of congenital TB should be considered in an infant with declining respiratory status not responsive to traditional therapies and/or a mother with risk factors. Neonatal providers need to be aware of the potential for congenital TB infection as the immigrant population in the United States continues to increase, many of whom originate from TB endemic countries.

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