

Review Article

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Management of newborn infant born to mother suffering from tuberculosis: Current recommendations & gaps in knowledge

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Tuberculosis (TB) is a global disease with increase in concern with growing morbidity and mortality after drug resistance and co-infection with HIV. Mother to neonatal transmission of disease is well known. Current recommendations regarding management of newborns of mothers with tuberculosis are variable in different countries and have large gaps in the knowledge and practices. We compare and summarize here current recommendations on management of infants born to mothers with tuberculosis. Congenital tuberculosis is diagnosed by Cantwell criteria and treatment includes three or four anti-tubercular drug regimen. Prophylaxis with isoniazid (3-6 months) is recommended in neonates born to mother with TB who are infectious. Breastfeeding should be continued in these neonates and isolation is recommended only till mother is infectious, has multidrug resistant tuberculosis or non adherent to treatment. BCG vaccine is recommended at birth or after completion of prophylaxis (3-6 months) in all neonates.

Key words Breastfeeding - congenital tuberculosis - perinatal transmission - prophylaxis - recommendations - therapy

Tuberculosis (TB) is a global public health problem, India and China together account for almost 40 per cent of the world's TB¹. Congenital infection by vertical transmission is rare with only 358 cases reported till 1995 and another 18 cases reported from 2001 to 2005². High neonatal mortality (up to 60%) and morbidity warrant early diagnosis and treatment of newborns suffering from TB. Existing guidelines for management of the newborns delivered to mothers with TB are variable and have no uniform consensus. An electronic search was carried out at PubMed and Google search engine. The search was limited to literature published in the last 10 yr in English language only. The reference lists

of all retrieved articles and guidelines were searched to further identify relevant articles. The key words used were "perinatal, neonatal, congenital, children, childhood, pregnancy, tuberculosis, management, treatment, guidelines" either singly or in different combinations. A manual search was done at both PubMed and Google for guidelines on tuberculosis by eminent organizations like World Health Organization (WHO), Centres for Disease Prevention and Control (CDC), American Academy of Pediatrics (AAP), Indian Academy of Pediatrics (IAP), Merck Manual, and national guidelines in countries like Britain National Institute for Health and Clinical Excellence (NICE),

New Zealand (NZ), Revised National Tuberculosis Control Programme (RNTCP) and Directly Observed Treatment Short course (DOTS) India, Southern African Society for Paediatric Infectious Diseases (SASPID) and Malaysian Thoracic Society (MTS) to have worldwide representation. Relevant articles which provided reasonable information regarding the concerned questions were also included.

Mother to infant transmission of TB

Congenital infection by vertical transmission of TB is described by transplacental transmission through umbilical veins to the foetal liver and lungs; or aspiration and swallowing of infected amniotic fluid *in utero* or intrapartum causing primary infection of foetal lungs and gut. Transplacental infection occurs late in pregnancy and aspiration from amniotic fluid occurs in the perinatal period. The diagnostic criteria used for congenital tuberculosis were as described by Beitzke in 1935³ and revised by Cantwell *et al* in 1994⁴. Cantwell *et al* proposed diagnosis of congenital tuberculosis in the presence of proven tuberculous disease and at least one of the following; (i) lesions in the newborn baby during the first week of life; (ii) a primary hepatic complex or caseating hepatic granulomata; (iii) tuberculous infection of the placenta or the maternal genital tract; and (iv) exclusion of the possibility of postnatal transmission by investigation of contacts, including hospital staff. In newborns diagnosed of TB, a horizontal spread in the postpartum period by droplet or ingestion from mother or undiagnosed family member is most commonly suggested. Transmission of tuberculosis through breast milk does not occur⁵.

Clinical manifestations of congenital tuberculosis

Infertility, poor reproductive performance, recurrent abortions, stillbirths, premature rupture of membranes and preterm labour are known effects of tuberculosis in pregnancy. The foetus may have intrauterine growth retardation, low birth weight, and has increased risk of mortality. The median age of presentation of congenital TB is 24 days (range, 1 to 84 days)⁴. Clinical manifestations are non specific and include poor feeding (100%), fever (100%), irritability (100%), failure to thrive (100%), cough (88.9%), and respiratory distress (66.7%). Examination reveals hepatosplenomegaly (100%), splenomegaly (77.8%), and abdominal distension (77.8%)⁶. Lymphadenopathy (38%) lethargy (21%), meningitis, septicaemia, unresolving or recurrent pneumonia, disseminated intravascular coagulation, jaundice, ascitis, otitis

media with or without mastoiditis (21%), parotitis, osteomyelitis, paravertebral abscess, cold abscess, and papular or pustular skin lesions (14%) are other known features⁷. Apnoea, vomiting, cyanosis, jaundice, seizures and petechiae have been reported in less than 10 per cent of cases⁸.

Investigations

Conventional methods: Diagnosis of TB in the newborn depends upon detailed history of maternal infection and high index of suspicion. Antenatal history by gynaecologists and trained nurses is beneficial in early diagnosis and determining neonatal outcome. Morphological and histological examination of placenta in suspected cases at the time of delivery is helpful. Screening of household contacts may yield source of infection. Clinical manifestations in neonates masquerade sepsis, prematurity, viral infections or other acute or chronic intrauterine infections and hence diagnosis is difficult and may be missed. Therefore, in the setting of poor response to antibiotics and supportive therapy, and negative results of microbiological evaluation and serological tests for acute and chronic intrauterine infections, TB should be suspected. Specimens from the neonate suitable for microscopy and culture include gastric aspirates, sputum (induced), tracheal aspirates (if mechanically ventilated), skin lesions, ear discharge, ascitic fluid, cerebrospinal fluid (CSF) and, pleural fluid (if present) for acid fast bacilli and cultured on standard egg based media for 12 wk)⁸⁻¹⁰. Bronchoalveolar lavage (BAL) is an important investigation and detection of *Mycobacterium tuberculosis* DNA in BAL fluid by polymerase chain reaction (PCR) is diagnostic in newborn¹¹. Liver or lymph node biopsy may be undertaken for histology and culture. Postmortem biopsies (*e.g.* liver, lung, nodes, and skin lesions) can also be done. Conventional light microscopy (Ziehl-Neelsen or Kinyoun stain) or fluorescence microscopy (auramine stain) are used for detection of *Mycobacterium*. Chest radiography and computed tomography may show the presence of scattered infiltrates, bronchopneumonia, consolidation or periportal hypodensity which are non specific. Mantoux test if positive, is supportive evidence, but negative results do not rule out disease. Multiple and repeated investigations may be done in view of high suspicion⁵.

Newer methods: Slow and tedious conventional methods have been recently replaced by quicker methods. The WHO has accredited LED (light emitting diode) fluorescence microscopy and liquid based mycobacteria

growth indicator tube (MGIT) in developed countries for fast results¹². Indirect methods include rapid interferon gamma assays, QuantiFERON-TB Gold assay and T-SPOT using antigens ESAT-6, CFP-10 and TB7 but have shown inconsistent results in newborns^{13,14}. Large trials using Gene Xpert (real time PCR) in children have been useful for rapid diagnosis in communities with a high burden of TB including multiple drug resistant (MDR) tuberculosis¹⁵. Other mycobacteriophage-based assays like Fast Plaque TB-Rif, molecular line probe assays (LPAs) such as GenoType MTBDR plus assay and the Inno-LiPA Rif TB assay are costly and with only a few studies in newborns^{16,17}.

Management of neonate born to mother with tuberculosis

When a woman suffering from tuberculosis gives birth, the aim is to ensure TB free survival of her newborn infant. It involves diagnosing active tubercular lesion including congenital tuberculosis, and treatment of the neonate or prevention of transmission of tubercular infection to the neonate from the mother. There is no uniformity as is evident from the recommendations of the eminent societies of different countries across the globe (Tables I and II).

(i) Prevention of transmission

(A) Maternal disease and therapy- Extrapulmonary, miliary and meningeal TB in mother are high risk factors for congenital TB in neonates²⁷. Vertical transmission from mothers with tubercular pleural effusion or generalized adenopathy does not occur⁵. However, there is a lack of scientific literature regarding increased risk of congenital TB if mothers have resistant TB or concurrent HIV infection. Mothers who have completed antitubercular treatment (ATT) before delivery or have received ATT for at least two weeks duration before delivery are less likely to transmit the disease to the newborn as compared to untreated mothers. Antitubercular drugs are found to be safe in pregnancy except streptomycin in the first trimester. No literature is available regarding the safety of second line antitubercular drugs used for resistant TB in pregnancy²⁸.

(B) Prophylaxis - The decision to start isoniazid (INH) prophylaxis to the neonate depends on a number of factors including the history of detection and duration of maternal disease (before or during or after pregnancy), type of tuberculosis (pulmonary or extrapulmonary), and maternal compliance of

treatment (regular or irregular). INH prophylaxis is recommended in the neonate if the mother has received treatment for <2 wk, or those who are on therapy for >2 wk but are sputum smear positive. In all other situations there is no need of therapy. American Academy of Pediatrics (AAP) recommends INH prophylaxis to all neonates of mothers who are diagnosed with tuberculosis in the postpartum period and/or after the commencement of breastfeeding has started as these newborns are considered potentially infected²⁰. Duration of prophylaxis is guided by skin testing by Mantoux test at three months in New Zealand²² and by WHO²¹, MERCK Manual²³ and AAP²⁰ or at 6 months in Malaysia and South Africa^{24,25}. If Mantoux test is negative, prophylaxis is stopped. However, if Mantoux test is positive and evidence of disease is found, ATT is started. If there is no evidence of disease in Mantoux positive neonates, then INH may be given for six months^{20,22} or 9 months²³. IAP does not comment on maternal treatment or Mantoux test and suggests isoniazid therapy to all newborns for at least 6-9 months or a minimum for three months until mother is culture negative¹⁸. There is also a variation in the dose recommended for prophylaxis with 5 mg/kg²⁴, 15 mg/kg²⁵, and 10 mg/kg^{20,23}.

(C) Nutrition and breastfeeding - Support for breastfeeding is crucial for the survival of the newborn. Human milk in addition to providing nutrition has immunological benefits and all efforts to continue breastfeeding in newborns with mothers having tuberculosis should be made. In case of maternal sickness or if mother is smear positive at the time of delivery or mothers with MDR TB, when breastfeeding may not be possible, expressed breast milk feeding is an alternative, with personal hygiene. AAP recommends continued feeding with expressed milk in mothers with pulmonary TB who are contagious, untreated or treated (< 3 wk) with isolation²⁰. WHO recommends feeding under all circumstances, however, close contact with the baby should be reduced²¹. Malaysian Thoracic Society recommends that if mother is contagious, efforts should be made to use expressed maternal milk for feeding²⁴. There is a paucity of scientific literature on the increased risk of neonatal transmission by breastfeeding in the presence of factors such as infection with resistant organisms (multiple or extensive drug resistance or co-infection with human immunodeficiency virus. First line ATT is secreted in milk in small quantity and causes no adverse effect on the child²⁹.

Table I. Comparison of recommendations on prophylaxis, diagnosis and treatment guidelines by different groups

	Diagnosis of congenital tuberculosis	Treatment of congenital tuberculosis	Prophylaxis	Follow up	Level of evidence
IAP ¹⁸	-		INH therapy (10 mg/kg) for 6 months after ruling out congenital TB		Not mentioned
DOTS/RNTCP ¹⁹	-	-	INH prophylaxis for 3 months. Do a Mtx test if negative, stop INH. If positive, search for TB and give treatment		Not mentioned
AAP ²⁰	Mtx, CXR, LP, appropriate cultures, placental histology	INH, rifampicin, pyrazinamide, streptomycin, kanamycin for 9-12 months. Corticosteroids in meningitis	INH for 3-4 months followed by Mtx test. If Mtx negative stop INH by 3 months. If Mtx is positive, a search for disease is made. If disease is positive then treat as congenital TB, if no disease give INH for 9 months	Monthly while on INH prophylaxis. Mtx to be repeated at 6, 9, 12 months. if Mtx is positive investigate for TB and continue INH	Not mentioned
WHO ²¹	Cantwell criteria		INH for 6 months. If Mtx negative, INH stopped. BCG after 2 weeks if Mtx is negative		Question not answered under level evidence
New Zealand guidelines on tuberculosis ²²	Mtx test, CXR, LP, cultures. microscopy and culture of gastric aspirate, biopsy tissue (lymph nodes, bone marrow, liver) or placental tissue. CSF also recommended	-	In asymptomatic infant INH (10 mg/kg) for 3 months. Mtx if neg, normal chest X-ray and asymptomatic child stop INH and give BCG. If positive asses for TB disease. If neg, INH for 6 months		Not mentioned
Merk Manual ²³	Culture of tracheal aspirate, CXR, Mtx. CSF, placental examination	INH, rifampicin, ethambutol and amikacin or kanamycin for first 2 months and INH, rifampicin for 6-12 months depending on disease category	INH for 3-4 months and then Mtx . After ruling out disease INH can be stopped. If Mtx is positive, but no disease then continue INH for 9 months under monitoring		Not mentioned

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	Diagnosis of congenital tuberculosis	Treatment of congenital tuberculosis.	Prophylaxis	Follow up	Level of evidence
MTS ²⁴	-	-	After ruling out congenital tuberculosis prophylactic INH treatment to infants born to mother with active pulmonary TB except those diagnosed more than 2 months before delievery and are documented with smear negative before delievery (Grade C). Prophylactic INH to be given for 6 months or alternatively 3 months of isoniazid followed by Mtx – if negative treatment stopped , if positive (> 5mm) treatment for 6 months followed by BCG (Level III). If mother is diagnosed of pulmonary TB after delievery, INH and rifampicin for 3 months or INH alone for 6 months may be given		Level III defined as opinion of respected authorities based on clinical experience, descriptive studies and case reports or reports of expert committees
SASPID ²⁵	-	3 drug regime or treat like military TB	INH (8-12mg/kg) for 6 months	Close follow up of children for clinical status adherence to INH prophylaxis	Not mentioned

IAP, Indian Academy of Pediatrics; DOTS, Directly Observed Treatment-short course; RNTCP, Revised National Tuberculosis Programme; AAP, American Academy of Pediatrics; WHO, World Health Organization; ATT, Antitubercular Treatment; BCG, Bacille Calmette-Guérin Vaccine; MTS, Malaysian Thoracic Society; SASPID, Southern African Society for Paediatric Infectious Diseases; MDR-TB, Multi Drug Resistant Tuberculosis; Mtx, Mantoux Test; PPD, Purified Protein Derivative Test (Tuberculin test)

(D) Isolation and barrier nursing – Isolation is recommended when mother is sick, non adherent to therapy or has resistant TB^{18,20,21} or received ATT four less than 2 wk^{19,24} or three weeks before starting ATT²⁰. Barrier nursing using face mask (20-22) and appropriate cough hygiene¹⁸ has been advised for the mothers who are breastfeeding. Hand washing, disinfecting nasal secretions and baby wipes are recommended by AAP²⁰.

(ii) Diagnosis, treatment and follow up

(A) Mantoux test - Utility of Mantoux test in neonates is poor due to low reactogenicity and poor helper T cell responses. In a study by Hageman *et al*³⁰ only two of the 14 infants with congenital TB had positive tuberculin tests. Current recommendations support use of Mantoux test after three months^{19,20,22} or six months²⁴. Exact cut-off (> 5, 5-10 and >10 mm) and strength of purified protein derivative (PPD)

Table II. Comparison of recommendations on isolation, breast-feeding and vaccination by different groups

Name of the group	Breast feeding	Barrier method	Isolation	BCG Vaccination	
IAP ¹⁸	Can continue to breast feed.	Cough hygiene	Not required if mother on treatment. Isolation if mother hospitalized, non-adherent to therapy or has MDR-TB.	Advised- at birth even with INH prophylaxis (IAP 2012)	Not mentioned.
DOTS ¹⁹	Feeding encouraged if mother sputum negative	Face mask	If mother has active disease and is noncompliant to treatment or has received ATT prior to delivery.	Vaccination may be postponed or done with INH resistant BCG vaccine.	Not mentioned.
AAP ²⁰	Breast feeding if mother is on ATT.	Face mask	Separation avoided. Advised if MDR-TB, non-compliant to therapy, mother has contagious TB before starting ATT.	Give BCG if mother has MDRTB, or poorly adherent to treatment	Not mentioned.
WHO ²¹	To continue	Face mask	If mother has MDR-TB.	Delay BCG until INH therapy is completed. BCG after 2 weeks of completing therapy	Question not answered under level evidence
New Zealand Guidelines On Tuberculosis ²²	Recommended irrespective of the maternal status	Mask and infection control measures	Separation till mother fully evaluated or until both are on treatment, if mother has MDR-TB or poor adherence to therapy. infant on isoniazid therapy needs no separation	BCG after 3 months of INH therapy	Not mentioned.
MERK MANUAL ²³	Breast feeding not contraindicated	=	Mother and baby should stay together.	If mother non adherent BCG should be given.	Not mentioned.
MTS ²⁴	Give expressed breast milk till mother sputum smear negative.	-	If mother smear positive at time of delivery.	BCG at birth if congenital TB ruled out. (level III) BCG should not be given to babies on prophylactic TB treatment(Grade C) After completing INH prophylaxis for 3 months mountoux if negative BCG administered or if positive BCG at 6 months. In babies born to mothers with active PTB < 2 months after deliver BCG may be repeated but no role of reimmunizing babies if mothers diagnosed of active pulmonary TB after 2 months of delivery. (level III)	Grade C recommendation defined as evidence from expert committee Reports , opinion and/or clinical experience of respected authorities, directly Indicates the absence of directly applicable clinical studies of good quality

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Name of the group	Breast feeding	Barrier method	Isolation	BCG Vaccination	
SASPID ²⁵	Mother should be encouraged to breast feed	-	-	BCG after 6 months of INH therapy or after completing treatment	Not mentioned.
NICE ²⁶	Breast feeding allowed	-	Mother and baby should not be separated	-	Not mentioned.

AAP, American Academy of Pediatrics; ATT, Antitubercular Treatment; BCG, Bacille Calmette-Guérin Vaccine; CDC, Centers for Disease Control and Prevention; DOTS, Directly Observed Treatment - short course; MDR-TB, Multi Drug Resistant Tuberculosis; MTx, Mantoux Test; PPD, Purified Protein Derivative Test (Tuberculin test); WHO, World Health Organization; MTS, Malaysian Thoracic Society; NICE, National Institute for Health and Clinical Excellence

(1 or 5 or 10 TU^{18,31}) in newborns. IAP in the recent recommendations has decreased the strength of PPD for skin testing to 2 TU³².

(B) Treatment – No specific treatment regimens for congenital tuberculosis are advised. Treatment includes isoniazid, rifampicin, ethambutol and kanamycin or amikacin for the first two months followed by isoniazid and rifampicin for 6-12 months²³ or similar to miliary tuberculosis²⁵ or isoniazid, rifampicin and pyrazinamide along with streptomycin and kanamycin for 9 to 12 months²⁰.

(C) Follow up - Neonates diagnosed and treated for congenital tuberculosis should be monitored while on therapy²¹, but no details regarding the timing or the modes of monitoring exist. DOTS¹⁹ recommends chest X-ray at the end of treatment. American Academy of Pediatrics suggested that infants receiving prophylaxis should have clinical surveillance²⁰. In a study periodic X-ray and Mantoux test have been advised at 6, 12 and 24 wk²⁸.

(iii) Long term protection

Bacillus Calmette Guerin (BCG) vaccination protects against the dissemination of tuberculosis and severe disease. In neonates with congenital tuberculosis there is no utility of BCG vaccine. In neonates receiving INH prophylaxis, BCG vaccine (timing not specified) is recommended^{18,19}. WHO recommends BCG vaccine until completion of INH therapy²¹. AAP has advised BCG vaccine after completion of chemoprophylaxis at six months or at birth along with isoniazid if follow up cannot be ensured²⁰. The New Zealand guidelines²² recommend BCG after three months of prophylaxis while in South Africa SASPID recommends it after six months of prophylaxis. MTS²⁴ recommends BCG

vaccination after ruling out congenital TB and again after the INH prophylaxis if scar is absent. Indian Academy of Pediatrics advises BCG vaccination at birth to all neonates after excluding congenital tuberculosis even if chemoprophylaxis is planned³². Hence it is evident that there is no consensus on the number, timing and interpretation of BCG vaccination in infants born to women with TB. In countries with significant number of TB patients in the community children are vulnerable to get TB infection early in life: Therefore, BCG vaccination as early as possible preferably after stopping of INH prophylaxis should be followed. There is an urgent need to conduct more studies to evaluate immunogenicity of BCG vaccine in infants receiving INH prophylaxis.

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