Tuberculosis in Neonates and Infants
Epidemiology, Pathogenesis, Clinical Manifestations, Diagnosis, and Management Issues

Chrysanthi L. Skevakhi and Dimitrios A. Kafetzis
Second Department of Pediatrics, 'P. and A. Kiriakou' Children's Hospital, University of Athens, Athens, Greece

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Tuberculosis is one of the leading infectious causes of death and as such represents a major global health problem. Infants may develop congenital tuberculosis from an infectious mother or, most commonly, they may acquire postnatal disease by contact with an infectious adult source. Important epidemiologic, pathogenetic, and clinical data regarding the management of infantile disease are reviewed.

Diagnostic evaluation includes tuberculin skin tests, chest radiography and other imaging studies, smears and cultures, examination of the cerebrospinal fluid, and polymerase chain reaction, as well as the more recent interferon-γ assay.

Pregnant women with a positive Mantoux skin test but normal chest x-ray should either start chemoprophylaxis during gestation or after delivery depending on the likelihood of being recently infected, their risk of progression to disease, as well as their clinical evidence of disease. Pregnant women with a positive Mantoux skin test and chest x-ray or symptoms indicative of active disease should be treated with non-teratogenic agents during gestation; all household contacts should also be screened. When tuberculosis is suspected around delivery, the mother should be assessed by chest x-ray and sputum smear; separation of mother and offspring is indicated only if the mother is non-adherent to medical treatment, needs to be hospitalized, or when drug-resistant tuberculosis is involved.

According to the American Academy of Pediatrics, treatment of latent infection is highly effective with isoniazid administration for 9 months. This regimen may be extended to 12 months for immunocompromised patients. When drug resistance is suspected, combination therapies, which usually consist of isoniazid with rifampin (rifampicin), are administered until the results of susceptibility tests become available. Organisms resistant to isoniazid only may be treated with rifampin alone for a total of 6–9 months.

All infants with tuberculosis disease should be started on four agents (isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin) until drug susceptibility is assessed. For susceptible intrathoracic tuberculosis, isoniazid, rifampin, and pyrazinamide are administered for a total of 2 months, at which point pyrazinamide is withdrawn and the other two agents are continued for another 4–10 months depending on the severity of the disease. The same regimen may be applied in extrapulmonary tuberculosis with the exception of skeletal, miliary, and CNS disease, which require daily administration of isoniazid, rifampin, pyrazinamide, and streptomycin for 1–2 months, followed by isoniazid and rifampin daily or twice weekly for another 10 months. When drug-resistant tuberculosis is suspected, a regimen of isoniazid, rifampin, and pyrazinamide plus either streptomycin or ethambutol should be initially prescribed, until the results of susceptibility tests become available. HIV-seropositive infants with pulmonary tuberculosis should receive isoniazid, rifampin, pyrazinamide, and ethambutol or an aminoglycoside for 2 months, followed by isoniazid and rifampin for a total of at least 12 months.

Apart from conventional antimycobacterial agents, novel therapeutic modalities, which stimulate the host immune system such as interleukin-2 (IL-2), IL-12, interferon-γ, and tumor necrosis factor antagonists have been tested with promising results.
million new cases of tuberculosis worldwide, compared with 8.4 million in 1999 and 8.0 million in 1997.\(^{[1,2]}\) Approximately 2 million deaths due to tuberculosis occur annually, which renders the disease the second most common infectious cause of death next to HIV infection.\(^{[3]}\) Currently, based on tuberculin sensitivity, more than one-third of the world’s population is infected with \textit{M. tuberculosis}.\(^{[4]}\)

Furthermore, it has been estimated that 1.3 million new cases and 450,000 deaths annually affect children under the age of 15 years;\(^{[5]}\) developing countries seem to bear the vast majority of the global disease burden. Epidemiologic data regarding congenital and postnatally acquired infantile tuberculosis are quite limited. However, perinatal tuberculosis seems to be rare,\(^{[6-9]}\) with fewer than 300 cases reported in the English-language literature (39 new cases have been reported since the last major review in 1980),\(^{[10-11]}\) in contrast with the incidence of postnatal disease in infants, which shows an escalating trend as a reflection of the global increase in tuberculosis over the last decade.\(^{[12]}\) Infants at high risk for tuberculous infection are shown in table I.

<table>
<thead>
<tr>
<th>Contacts of adults with infectious tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection or other immunosuppressive condition</td>
</tr>
<tr>
<td>healthcare workers dealing with high-risk patients</td>
</tr>
<tr>
<td>intravenous drug user</td>
</tr>
<tr>
<td>homelessness, low socioeconomic status in certain areas</td>
</tr>
<tr>
<td>residents of correctional institutions or nursing homes</td>
</tr>
<tr>
<td>migrant workers</td>
</tr>
<tr>
<td>Parents or infant from high prevalence countries</td>
</tr>
<tr>
<td>HIV infection or other immunosuppressive condition (malnutrition, organ failure, neoplastic disease etc.)</td>
</tr>
</tbody>
</table>

2. Pathogenesis

In order for postnatal tuberculosis to occur, an infant must be first significantly exposed to a contagious adult. Airborne transmission of infective droplets is the most common mode of incula-
tion. In this ‘exposure’ stage the child has a negative tuberculin skin test, a normal chest radiograph, and no related symptoms or signs. Following inhalation of the bacilli, a primary complex is formed consisting of a peripheral lobar lesion and involvement of the regional lymph nodes (usually the hilar nodes) through the lymphatic system. In the vast majority of cases, the initial lesion heals and calcifies, producing a Ghon lesion on chest radiography. During primary complex formation, tubercle bacilli may disseminate lymphohematogenously to pulmonary as well as extrapulmonary sites such as the pleura, pericardium, lymph nodes, CNS, bones and joints, skin, and gastrointestinal and genitourinary systems. As a rule, this metastatic seeding becomes constrained but in some cases it may lead to the development of extrapulmonary disease: either primary tuberculosis (months to years later) or reactivation of tuberculosis (several years later). Infants develop only primary tuberculosis (absence of any pre-existing immunity) in contrast with adults who can develop post-primary disease, which occurs when individuals have pre-existing immunity to mycobacterial antigens. Tuberculosis ‘infection’ is present if a symptom-free infant has conversion of skin test reactivity from negative to positive and either a normal chest roentgenogram or one with granuloma or calcification in the lung parenchyma or regional lymph nodes. Finally, tuberculosis ‘disease’ is the development of associated symptoms or signs or of a characteristic radiographic picture, which, in the case of neonates, may occur within months from the primary infection.[20]

Hematogenous spread from mother to fetus during pregnancy leads to the formation of one or more primary complexes in the liver, with involvement of the periportal lymph nodes, or in the lungs.[13] The bacilli sometimes remain dormant in the lungs and start to multiply right after birth when oxygenation and circulation are greatly enhanced, leading to active disease.[13] Aspiration or ingestion of contaminated amniotic fluid creates multiple primary complexes in the lung, gut, or middle ear.[28]

To date, two distinct sets of criteria have been proposed in an attempt to define true congenital tuberculosis. According to the first, established by Beitzke[29] in 1935, the infant must have proved tuberculous lesions and one of the following should apply: lesions in the first few days of life, a primary hepatic complex, or the exclusion of the possibility of postnatal transmission by the separation of the infant at birth from the mother and other sources of infection. Subsequently, Cantwell et al.[8] projected revised diagnostic criteria, which apply more easily in current practice (see table II).

### Table II. Revised diagnostic criteria for congenital tuberculosis[8]

<table>
<thead>
<tr>
<th>Proved tuberculous lesions and at least one of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>lesions in the first week of life</td>
</tr>
<tr>
<td>a primary hepatic complex or caseating hepatic granulomas</td>
</tr>
<tr>
<td>tuberculous infection of the placenta or the maternal genital tract</td>
</tr>
<tr>
<td>exclusion of the possibility of postnatal transmission by a thorough investigation of contacts, including the infant’s hospital attendants, and by adherence to existing recommendations for treating infants exposed to tuberculosis</td>
</tr>
</tbody>
</table>

### 3. Clinical Manifestations

Symptoms of congenital tuberculosis disease begin sometime from birth up to 4 months of age, most commonly around the second or third week of life.[8,30] Often the clinical features of infantile tuberculosis are atypical mimicking other conditions such as congenital viral infections and sepsis;[31-33] therefore, a high index of suspicion is required in order to reach the diagnosis. The most frequent symptoms and signs of congenital tuberculosis upon presentation are: hepatosplenomegaly, respiratory distress, fever, lymphadenopathy, abdominal distension, lethargy, irritability, ear discharge, and papular skin lesions.[8] Less frequent symptoms appear to be vomiting, apnea, cyanosis, jaundice, seizures, and petechiae, which occur in ≤10% of patients.[8] Similar symptomatology has been reported for infants with disease acquired after birth.[12] Respiratory signs include tachypnoea, stridor, wheeze, crepitations, and bronchial breathing.[20]

Specific clinical manifestations of either pre- or postnatally acquired tuberculosis naturally depend on the site and severity of tuberculous lesions as well as on the time since infection. All possible forms encountered in adults, both pulmonary and extrapulmonary, may occur, although with different frequencies compared with those in older age groups. As mentioned in section 1.3, disseminated and meningeal forms of the disease occur more frequently in infants, which may be, at least partially, attributed to the intrinsic immaturity of their immune system.

Mediastinal lymph node tuberculosis may easily result in compression of the infants’ small Airways with subsequent signs suggestive of bronchial obstruction and air entrapment such as wheezing and decreased respiratory sounds.[20,24] Superficial tuberculous lymphadenitis most commonly affects the submandibular and anterior cervical nodes with fever and associated lymph node enlargement upon presentation. Tuberculous involvement of the CNS may present as meningoencephalitis, basal arachnoiditis, or intracranial tuberculosis.[34] Meningitis usually manifests with fever, cough, nuchal rigidity, vomiting, alteration of conscious-
ness, and refusal to feed. Less common manifestations are a bulging anterior fontanel and generalized seizures. As for miliary tuberculosis, common signs and symptoms include fever, cough, failure to thrive, hepatosplenomegaly, and respiratory distress.

4. Diagnosis

Diagnostic evaluation of an infant with tuberculosis disease is rather challenging if one considers the non-specific nature of the associated symptoms and signs. A high index of suspicion must be therefore maintained in particular contexts (see table I). In the case of congenital disease, failure to respond to antibiotic therapy as well as exclusion of other congenital infections are further indications for tuberculosis evaluation.

Moreover, assessment of patients for tuberculosis differs between developed and developing countries as the latter lack the resources for advanced laboratory-based diagnosis and sophisticated imaging techniques. Diagnosis in these areas depends primarily upon history, skin testing, and conventional chest x-ray. Nevertheless, India’s tuberculosis control program, which was introduced in 1993 and improved the quality of diagnosis apart from other new policies implemented, may serve as a paradigm of wise allocation of funds in a country with low economic development.[35] This program had a tremendous impact on morbidity and mortality due to tuberculosis and indirectly produced significant cost savings.[35]

4.1 Tuberculin Skin Tests

There are two major techniques for tuberculin skin testing: the Mantoux test and the multiple puncture tests. However, the latter are associated with several disadvantages such as non-standardization of the amount of antigen introduced, the need for a subsequent Mantoux test in the case of positivity (which is further complicated by the ‘booster phenomenon’), and high rates of false-positive and false-negative results.[36] Furthermore, their widespread use led to the practice of allowing non-professionals such as parents to interpret the skin test results and report them to the physician, which is often misleading.[36] Therefore, the Centers for Disease Control and the American Thoracic Society have suggested that the use of multiple puncture tests should be restricted or even completely abandoned.

A positive Mantoux test at 72 hours indicates infection with *M. tuberculosis*; tuberculin sensitivity develops 3 weeks to 3 months after inhalation of the bacilli and remains for the child’s lifetime. Following bacillus Calmette-Guérin (BCG) vaccination, an infant may or may not develop tuberculin reactivity. For those who convert, the induration size is usually <10mm and wanes after approximately 3 years.[37] Recently, an *in vitro* assay of whole blood for cell-mediated immunity has appeared quite promising for distinguishing between tuberculous infection and BCG reactivity.[38] This assay is based on the release of interferon-γ (IFNγ) from T lymphocytes in response to stimulation with the secreted antigen ESAT-6, which is absent in the BCG vaccine.

In general, a Mantoux skin test reaction of ≥10mm in children aged <4 years (this age group is regarded to be at increased risk for dissemination) is considered positive, independent of immunization status[38,39] (table III). The respective cutoff value for infants in close contact with a known or suspected infectious case of tuberculosis, for those clinically or radiographically suspected to have tuberculous disease, and for immunosuppressed infants is 5mm. A variety of factors including young age and severe forms of tuberculosis may diminish reactivity to tuberculin,[40] which means that a negative Mantoux result in infants does not in any case exclude the possibility of tuberculosis.

4.2 Chest Radiography

A chest x-ray is an invaluable diagnostic tool in tuberculosis disease as abnormal features are almost always exhibited. Common manifestations among infants include: (i) hilar or paratracheal adenopathy; (ii) infiltrate; (iii) hilar or paratracheal adenopathy plus infiltrate; (iv) miliary pattern; (v) miliary pattern plus pleural effusion; (vi) pleural effusion; and (vii) mediastinal adenopathy.[41] Compression of the trachea, bronchi, or both with resultant atelectases is also quite frequent.[12,20,42] Tuberculous lesions may be located in any lung segment, although a recent study[43] suggests that upper lobes and posterior segments are the most common sites for tuberculosis in infants aged <1 year. In general, individuals who are standing at the time of infection develop a primary focus in the right lower lobe of the lung, whereas those who are recumbent develop a primary focus in the posterior

<table>
<thead>
<tr>
<th>Table III. Definition of a positive Mantoux skin test (5 TU-PPD) in infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction ≥5mm</td>
</tr>
<tr>
<td>Infants in close contact with a known or suspected infectious case of tuberculosis</td>
</tr>
<tr>
<td>Infants with abnormal chest x-ray</td>
</tr>
<tr>
<td>Infants with clinical evidence of tuberculosis</td>
</tr>
<tr>
<td>Immunosuppressed infants (HIV infection or other immunosuppressive condition)</td>
</tr>
<tr>
<td>Reaction ≥10mm</td>
</tr>
<tr>
<td>All infants without any risk factors</td>
</tr>
</tbody>
</table>

TU-PPD = tuberculin units of purified protein derivative.
segments of the upper lobes. Nevertheless, it should be emphasized that a normal chest radiograph does not necessarily rule out the presence of tuberculosis or even miliary disease, which may develop within the subsequent days.\(^{41,44}\)

4.3 Other Imaging Studies

Plain radiography, ultrasound, CT, and magnetic resonance imaging (MRI) are all important components of the diagnostic armamentarium for tuberculosis in infants.\(^{42,45,46}\) These imaging techniques were reported to be indispensable in the early assessment and guided aspiration of a rare case of perinatal/congenital spine tuberculosis accompanied by paravertebral abscess.\(^{45}\) Thoracic CT is especially helpful in infants because of better visualization of adenopathies compared with chest x-ray. Abdominal sonography has been used in guided biopsy of hepatic foci; this technique has revealed caseating granulomas with tubercle bacilli and led to the diagnosis of congenital tuberculosis.\(^{47,48}\) Ultrasound, CT, and MRI have also been used in the diagnosis of tuberculosis of the CNS.

4.4 Smears/Cultures

Specimens for smear or culture can be obtained from early morning gastric aspirate, (induced) sputum, cerebrospinal fluid (CSF), tracheal/bronchial aspirate, ear discharge, urine, peritoneal fluid, and biopsy of skin, liver, bone marrow, or lymph node, depending on the location of the lesion.\(^{18,20}\) Cultures take about 6–12 weeks for results to be obtained, which limits the speed of reaching a definitive diagnosis and thus impedes timely initiation of appropriate therapy. Moreover, microbiologic confirmation of infection is established in only a relatively small proportion of patients (larger though in infants when compared with older children) with gastric fluid being the most common biologic fluid tested. Despite the low sensitivity associated with cultures, specificity reaches 100% once positive.

4.5 Polymerase Chain Reaction

Polymerase chain reaction (PCR) assays are both sensitive and specific for the detection of \(M.\) tuberculosis in adults and they provide results within 1–3 days.\(^{49}\) However, the available assays have limited applicability with gastric aspirates\(^{50}\) and a lower yield in infants in whom the bacillary burden is low; thus, the need for culture is of highest priority in this age group. Furthermore, due to the extreme sensitivity of PCR, strictly sterile conditions should be maintained throughout collection, transportation, and testing in order to avoid crossover contamination and false-positive reactions.

4.6 Examination of the Cerebrospinal Fluid

Tuberculosis of the CNS in infants is associated with characteristic findings in the CSF, which may contribute to the diagnosis. More specifically, lymphocytic pleocytosis, increased protein levels, and decreased CSF/serum glucose ratio are the most typical features.\(^{51}\)

4.7 Alternative Tests

Neopterin is a product of human macrophages that is released upon stimulation by IFN\(\gamma\) and indicates cellular immune activation. According to a study,\(^{52}\) infants with uncomplicated primary tuberculosis disease and a good response to therapy demonstrated no or slightly elevated neopterin levels compared with excessive neopterin levels exhibited in infants with progressive primary tuberculosis.

According to a number of articles,\(^{53-55}\) measurement of adenosine deaminase activity and IFN\(\gamma\) levels in pleural fluid improves the diagnosis of tuberculous pleurisy, with the latter alone having the highest sensitivity and specificity when compared with other biologic markers.\(^{56}\)

5. Antituberculous Medications

Commonly used antituberculosis drugs are presented in table IV and agents used in the treatment of drug-resistant tuberculosis are presented in table V.

5.1 Isoniazid

Isoniazid, a hydrazide of isonicotinic acid available in both oral and parenteral (intramuscular) formulations, is highly bactericidal for \(M.\) tuberculosis. It inhibits the enzyme mycolase synthetase, which produces mycolic acid, and results in the disruption of the mycobacterial cell wall.\(^{58}\) It has also been suggested that isoniazid affects alterations in lipid levels, synthesis of nucleic acids, and production of adenosine triphosphate.\(^{58}\)

Isoniazid is inexpensive, readily absorbed from the gastrointestinal tract when given on an empty stomach, and diffuses extensively into all body tissues and fluids. Metabolism occurs through acetylation in the liver and the rate of this process shows genetic polymorphism. Neither drug efficacy nor adverse reactions such as hepatotoxicity seem to correlate with the acetylation status of a child.\(^{59,60}\) However, full maturity of the enzymatic pathways...
### Table IV. Commonly used antituberculosis drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Daily dose (mg/kg)</th>
<th>Twice-weekly dose (mg/kg/day)</th>
<th>Maximum dose</th>
<th>Major adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid(^a,b)</td>
<td>PO, IM</td>
<td>5–10</td>
<td>20–30</td>
<td>Daily: 300mg</td>
<td>Elevation of transaminase levels, GI disturbance (PO), rash, hematologic, metabolic, neurologic (agitation, seizures, ataxia), and psychiatric (psychosis) events, and hypersensitivity reactions (very rarely)</td>
<td>Pyridoxine serves as an antidote in cases of acute overdose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Twice weekly:</td>
<td>900mg</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin (rifampicin)(^a,b)</td>
<td>PO, IV</td>
<td>10</td>
<td>10–20</td>
<td>600mg</td>
<td>Elevation of transaminase levels, GI disturbance, thrombocytopenia, headache, dizziness, fatigue, pruritus, rash, renal failure, flu-like syndrome, orange discoloration of urine, sweat, and tears</td>
<td>Interacts with many drugs (e.g. theophylline, phenytoin, paracetamol, carbamazepine etc.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide(^b)</td>
<td>PO</td>
<td>35</td>
<td>50</td>
<td>2g</td>
<td>Elevation of transaminase levels, GI disturbance, hyperuricemia (usually without symptoms in infants), photosensitivity, fever, rash</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>PO</td>
<td>15</td>
<td>50</td>
<td>2.5g</td>
<td>Optic neuritis, GI disturbance, hyperuricemia, hypersensitivity reactions</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>IM</td>
<td>20–40</td>
<td>20–40</td>
<td>1g</td>
<td>Ototoxicity, nephrotoxicity, bone marrow suppression</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isoniazid (150mg) and rifampin (300mg) are combined in a capsule preparation called Rifamate\(^b\) (the use of trade names is for product identification purposes only and does not imply endorsement).

\(^b\) Isoniazid (50mg), rifampin (120mg), and pyrazinamide (300mg) are combined in a tablet formulation called Rifater\(^b\).

**GI** = gastrointestinal; **IM** = intramuscular; **IV** = intravenous; **PO** = oral.
Table V. Agents used in the treatment of drug-resistant tuberculosis[\textsuperscript{67}]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Dose (mg/kg/day)</th>
<th>Maximum dose (g)</th>
<th>Major adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide</td>
<td>PO</td>
<td>15–20 (two or three divided doses)</td>
<td>1</td>
<td>GI disturbance, hepatotoxicity</td>
<td>Bacteriostatic, penetrates blood-brain barrier</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>PO</td>
<td>5–50</td>
<td>0.3</td>
<td>GI disturbance, elevation of aminotransferase levels, discoloration of body secretions, hematologic abnormalities</td>
<td>Interacts less with protease inhibitors compared with rifampin</td>
</tr>
<tr>
<td>Kanamycin/ capreomycin</td>
<td>IM</td>
<td>15–30</td>
<td>1</td>
<td>Renal toxicity, ototoxicity</td>
<td>Bactericidal, no cross-resistance with streptomycin</td>
</tr>
<tr>
<td>Amikacin</td>
<td>IV</td>
<td>15–30</td>
<td>1</td>
<td>Renal toxicity, ototoxicity</td>
<td>Bactericidal, no cross-resistance with streptomycin</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>PO</td>
<td>10–20 (two divided doses)</td>
<td>1</td>
<td>Neuropsychiatric disturbances</td>
<td>Requires pyridoxine supplementation and monitoring of serum drug concentrations</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>PO, IV</td>
<td>PO: 20–30 (two divided doses)</td>
<td>PO: 1.5</td>
<td>Destruction of growing cartilage in animals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV: 15–20 (two divided doses)</td>
<td>IV: 0.8</td>
<td>Destruction of growing cartilage in animals</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>PO</td>
<td>400–800 (two divided doses)</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>PO</td>
<td>200–300 (three or four divided doses)</td>
<td>10</td>
<td>GI disturbance, hepatotoxicity</td>
<td></td>
</tr>
</tbody>
</table>

GI = gastrointestinal; IM = intramuscular; IV = intravenous; PO = oral.

responsible for isoniazid metabolism is not reached until 4 years of age; therefore, the incidence of the fast acetylator phenotype increases with age.\textsuperscript{61} The route of elimination of metabolites of isoniazid is primarily renal.

Because isoniazid is a competitive inhibitor of pyridoxine metabolism, this drug may cause peripheral neuritis or convulsions. Therefore, infants who are breastfeeding, as well as those who are malnourished, predisposed to neuropathy (those with diabetes mellitus, uremia), or have symptomatic HIV infection should receive pyridoxine supplements at a dosage of 0.5–1 mg/kg/day.\textsuperscript{[20,62,63]} Three to ten percent of children receiving isoniazid treatment exhibit an asymptomatic transient elevation of serum transaminase levels (not necessarily attributable to the administration of isoniazid). Clinically manifested hepatotoxicity is quite rare and occurs more frequently with dosages exceeding 10 mg/kg/day.\textsuperscript{[64,65]} co-administration of rifampin (rifampicin), pre-existing underlying hepatic disease, and also with severe forms of tuberculous disease. In children, monitoring of biochemical parameters during treatment is indicated only when aggressive high-dose or concurrent hepatotoxic therapy is being administered. Routine monitoring of symptoms and signs of hepatotoxicity is recommended in all cases and isoniazid should be discontinued immediately if they develop. In addition, withdrawal, at least temporarily, should be considered if liver enzyme levels exceed three to five times their upper limit of normal.\textsuperscript{[62]}

5.2 Rifampin (Rifampicin)

Rifampin is available in oral and intravenous forms and acts by binding to and thus inhibiting the β-subunit of the bacterial DNA-dependent RNA polymerase.\textsuperscript{[68]} It is bactericidal against both intra- and extracellular mycobacterial populations. Rifampin is a lipid-soluble agent that is readily absorbed via the oral route and distributes extensively in tissues and body fluids. Rifampin is available in 150mg and 300mg capsules, which are doses not appropriate for infants. Suspensions of 10 mg/mL have variable potency; the most accurate is the one produced from the intravenous form whereas the suspension produced from the capsule does not achieve 90% of the labeled potency until 7–14 days after preparation.\textsuperscript{[66]} Excretion occurs primarily through the biliary tract and secondarily through the urinary tract.
5.3 Pyrazinamide

Pyrazinamide, a synthetic analog of nicotinamide, is characterized by potent sterilizing activity in the acidic intracellular pH. This drug is rapidly absorbed and distributed. The available tablets of 500mg are unsuitable for young infants since the recommended dosage is 35 mg/kg/day. Suspensions of 100 mg/mL have been shown to be stable for 2 months. Elimination of pyrazinamide takes place through glomerular filtration.

5.4 Ethambutol

Ethambutol is bacteriostatic at a dosage of 15 mg/kg/day and bactericidal at 25 mg/kg/day. Its main use is as a companion drug in various treatment regimens for tuberculosis, in order to prevent the emergence of resistant strains to other drugs. Ethambutol acts by interfering with cell metabolism and ultimately with mycobacterial RNA synthesis. It may also play a role in the production of the cell wall glycolipid arabinogalactan. In adults, ethambutol is well absorbed through the gastrointestinal tract, penetrates the blood-brain barrier, undergoes extensive distribution, and is finally excreted, partly unchanged, in the urine and feces. The most serious adverse effect of this drug is optic neuritis with resultant decreased visual acuity, central scotoma, and red/green color blindness (unilateral or bilateral). The risk of optic neuritis is both dose and duration dependent. This effect, although rarely reported in children, has raised particular concern regarding the use of ethambutol in infants, since vision cannot be adequately examined in this population and early visual changes cannot be detected in a timely manner. On the other hand, ethambutol is usually administered for only 2 months until results of susceptibility tests are available; the possibility of development of optic neuritis is very small during such a limited period. Therefore, it has been suggested that ethambutol may be used safely in cases of life-threatening forms of tuberculosis or drug-resistant tuberculosis.

5.5 Streptomycin

Streptomycin is bactericidal for extracellular mycobacteria but it has little activity on bacilli located inside macrophages where the pH is low. Streptomycin is only available in a parenteral form; this is associated with some inconvenience, discomfort, as well as the extra treatment-associated costs. The recommended starting pediatric dosage is 20–40 mg/kg/day but it should be determined by peak and trough blood interactions. As with ethambutol, the use of streptomycin is limited to initial treatment regimens when drug-resistant tuberculosis is suspected or severe forms of the disease are present.

5.6 Other Drugs

Several other drugs have antituberculous activities but are considered second-line agents because of their greater toxicity or lesser efficacy compared with the drugs mentioned in sections 5.1–5.5. The most important characteristics of these medications are summarized in table V.

6. Future Therapeutic Modalities

As the prevalence of multidrug-resistant tuberculosis is increasing worldwide, the need for new therapeutic strategies and agents is becoming imperative. In the last few years, a significant amount of research has focused on methods that stimulate the host immune system and enhance its capacity to eradicate mycobacteria. Interleukin-2 (IL-2), IL-12, IFNγ and tumor necrosis factor (TNF) antagonists have all been used in the treatment of adults with tuberculosis, with promising results. The role of TNF in the pathogenesis of active disease has not been fully elucidated. TNF levels are high in the early stages of the disease and then decrease as the patient recovers, and may thus contribute to the protective host immunity against M. tuberculosis. However, at the same time, high levels of TNF have been implicated in the pathogenesis of the fever, cachexia, and weakness associated with tuberculosis. Further studies are required to establish the efficacy of these immunotherapeutic approaches and to determine their role in the treatment of tuberculosis in adults and children.

Apart from strategies that aim to stimulate the host response against tubercle bacilli, another promising approach, yet largely unexplored, appears to be one that will enable delivery of high concentrations of antituberculous agents directly to the lungs thereby avoiding systemic toxicity.

7. Therapeutic Drug Monitoring

Therapeutic drug monitoring allows the physician to adjust drug dosages early in the course of treatment, in order to achieve therapeutic serum drug concentrations and prevent the emergence of drug resistance as well as the development of serious toxicity. Therapeutic drug monitoring is indicated for patients who are slow responders to antituberculous regimens, receive additional drugs for other medical reasons and are therefore at risk of drug-drug interactions, have drug-resistant disease and are receiving second-line antituberculous agents, and also for patients with coexisting...
diseases that interfere with the absorption or elimination of administered drugs.\textsuperscript{178}

Since the pharmacokinetics of most antituberculous drugs in infants are essentially unknown, and most of the relevant data are extrapolated from studies in adults and older children, therapeutic drug monitoring is an invaluable ally in the treatment of tuberculosis in this specific subpopulation of patients.

8. Management Issues

8.1 Perinatal Tuberculosis

An evaluation algorithm for pregnant women at high risk for tuberculosis is presented in figure 1 while a management algorithm for the mother and newborn when tuberculosis is suspected at delivery is presented in figure 2. In order to prevent perinatal tuberculosis, high-risk pregnant women should undergo tuberculin skin testing. In the case of a positive result, chest radiography with appropriate abdominal shielding must be performed (see also table 1).\textsuperscript{179}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{algorithm.png}
\caption{Evaluation algorithm for pregnant women at high risk for tuberculosis.\textsuperscript{132} \textsuperscript{CXR} = chest x-ray.}
\end{figure}

8.1.1 Pregnant Women with Positive Mantoux Skin Test But Normal Chest X-Ray

If infected pregnant women (positive Mantoux skin test) have no clinical or radiographic evidence of tuberculosis disease, the infant does not need to be separated from her after delivery and does not require any special evaluation or treatment if the infant remains asymptomatic. Suitable chemoprophylaxis for the mother (commonly isoniazid alone), along with vigilant monitoring for the development of symptoms or radiographic findings suggestive of active disease, should be initiated during pregnancy if recent infection is likely or if she is considered to be at increased risk for progression to disease (i.e. malnourished, HIV infected, immunocompromised or undergoing immunosuppressive therapy). Recent infection is probable if the mother has conversion of skin reactivity from negative to positive within the past 2 years or has recently been in contact with an infectious source. If recent infection is not probable and the mother is not at increased risk for progression to disease, treatment for latent tuberculosis infection may be started after delivery under the condition that chest radiographs remain normal. Other members of the family should be tested and evaluated thoroughly. If disease is suspected or verified within the
Fig. 2. Management algorithm for the mother and newborn when tuberculosis is suspected at delivery. CXR = chest x-ray.

infant's environment, skin testing will be required for the infant as well.

8.1.2 Pregnant Women with Positive Mantoux Skin Test and Abnormal Chest X-Ray

If infected pregnant women (positive Mantoux skin test) are symptom free and have an abnormal chest radiograph, which is compatible with inactive tuberculosis (calcified or fibrotic lesions), treatment should be postponed until after delivery. No separation of the mother and newborn is required but all family members and contacts should be evaluated.

A positive Mantoux test along with the presence of related symptoms or a radiograph consistent with active disease in a pregnant woman demands further evaluation with sputum smears and cultures and initiation of appropriate therapy with non-teratogenic agents. Screening of household members should never be omitted.

When tuberculous disease is suspected in a pregnant woman at delivery, the neonate must be separated from the mother until a chest radiograph of the mother becomes available. If the radiograph is abnormal, the infant should remain separated from the mother until she is meticulously evaluated. The next essential step for evaluation of the mother is sputum examination for detection of acid-fast bacilli. At the same time, all members of the family and contacts should be investigated for tuberculosis infection or disease.

If the mother has an abnormal roentgenogram but no radiographic evidence of active disease, and this is also supported by the history, physical examination, and sputum smear, the infant is considered to be at low risk for infection, does not need to be isolated from the infected mother, and does not require treatment with antituberculous agents. The mother should be asked whether she has received previous antituberculous chemotherapy and should be given appropriate therapy (if she has not been previously treated) in order to prevent exposure of the infant to reactivation disease of the mother.

On the other hand, if the mother is thought to be contagious based on clinical, radiographic, and sputum evidence, the infant should be, in addition to being isolated from the mother, evaluated for congenital tuberculosis by means of clinical assessment and radiography. HIV serology should be also performed for the mother and neonate. If the newborn has no evidence of tuberculosis, isoniazid therapy (a single dose of 10 mg/kg daily) should be immediately initiated for the infant while the mother is being treated for active disease. Once therapy is started, further separation of the mother and infant (until the mother is proved to be non-infectious) is only indicated if the mother requires hospitalization, if non-adherence to the treatment regimen is suspected, or if drug-resistant strains of M. tuberculosis are implicated. Isoniazid therapy of the newborn should be sustained until the mother is sputum and culture negative for 3 months. Before discontinuation, a
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Mantoux test repeated after 6-12 months. If the test is negative, isoniazid treatment may be discontinued with a positive, therapy should be continued for a total of 9-12 months. If tuberculin skin test should be performed on the infant; if it is non-reactive to tuberculin, treatment may be discontinued; if the test is positive, the full course of therapy should be administered. If the infants remain non-reactive to tuberculin, treatment may be discontinued; if the test is positive, the full course of therapy should be administered. Evidently, it is very important, based on the child's history of contacts, to distinguish between a positive tuberculin response reflecting 'latent' disease and tuberculin sensitivity coexistent with primary tuberculosis. If a child who has active disease is treated with isoniazid chemoprophylaxis, the child might later develop more serious progressive primary tuberculosis and treatment could then be problematic if isoniazid resistance has developed.

The treatment of choice for latent tuberculous infection or recent exposure in infants who have not been previously treated is monotherapy with isoniazid. According to current recommendations isoniazid should be administered for 9 months. This regimen has been shown to reduce the incidence of tuberculous disease by 90% during the first year after treatment, and the protective effect has been reported to last for at least 30 years. Isoniazid is administered daily as a single dose of 10 mg/kg (300 mg/kg is the maximum dose). However, when adherence to daily therapy is suspected to be poor, isoniazid may be given twice weekly under direct observation after 1 month of daily treatment. In this case, each dose should be 20-40 mg/kg (maximum dose 900 mg/kg). Directly observed therapy (direct observation of a patient by a healthcare worker while the patient ingests the medication) prevents the consequences of poor adherence (i.e. treatment failure, relapse, and secondary drug resistance). For infants with HIV coinfection or any immunosuppressive condition, treatment should be continued for a minimum of 12 months.

When latent infection with drug-resistant strains of *M. tuberculosis* is suspected, an initial regimen of isoniazid together with rifampin is recommended until the results of susceptibility tests of isolates from either the infant or the adult contact are available. Drug resistance is suspected when the patient lives or was born in a country with a high prevalence of resistant strains, and when the adult source has documented drug-resistant tuberculosis or positive smears/cultures after 2 months of antituberculous therapy or a history of previously under-treated disease. If the results of susceptibility testing prove that the responsible organism is isoniazid resistant only (or if the drug cannot be tolerated by the patient), isoniazid should be discontinued and rifampin should be administered for a total of 6-9 months. Rifampin can also be given on a daily or a twice-weekly basis. Regarding isolates resistant to both isoniazid and rifampin, optimal therapy has not yet been established. Suggested regimens include the combination of a fluoroquinolone with pyrazinamide or high-dose pyrazinamide and ethambutol for 6-9 months. Finally, for bacilli resistant to multiple drugs an expert in pediatric tuberculosis should be advocated; the most common strategy is to prescribe two drugs to which the organism is susceptible.

8.3 Treatment of Tuberculosis Disease in Infants

8.3.1 Drug-Susceptible Intrathoracic Tuberculosis

The optimal management of tuberculosis requires treatment regimens that combine the shortest possible duration with the highest efficacy. Short-course regimens decrease the emergence of secondary drug resistance, reduce the total cost of treatment, and improve patients’ adherence. Congenital and acquired tuberculosis disease in infants should be treated similarly.
Upon suspicion of active disease, infants should be started on four anti-tuberculous medications (isoniazid, rifampin, pyrazinamide, plus either ethambutol or streptomycin) until the organism is known to be fully susceptible to all agents used. Current recommendations for drug-susceptible pulmonary tuberculosis with or without intrathoracic adenopathy and for hilar adenopathy alone in infants suggest the use of isoniazid (10–15 mg/kg/day), rifampin (10–20 mg/kg/day), and pyrazinamide (15–30 mg/kg/day) for 2 months, followed by at least 4 months of isoniazid and rifampin. The continuation phase of the therapeutic regimen may be extended to 10 months depending on the severity of the disease. With the aforementioned regimen, treatment may be administered twice weekly right from the beginning or after a phase of half a month, 1 or 2 months-long daily therapy, preferably under direct observation; the success rate of this regimen approaches 100%.

A study using isoniazid (10–15 mg/kg/day) and rifampin (10–15 mg/kg/day) with or without streptomycin (30 mg/kg/day) daily for 15 days followed by similar doses of isoniazid and rifampin twice a week for another 8.5 months suggested this regimen was safe and effective for treating tuberculosis in young infants aged <6 months. Some centers prefer to administer isoniazid and rifampin without streptomycin for a total of 9 months when drug resistance is considered rather unlikely. Again, this course can be given daily initially, and then twice weekly.

8.3.2 Extrapulmonary Tuberculosis

Antituberculous agents have excellent tissue penetration; moreover, only small numbers of mycobacteria are usually present at extrapulmonary sites of infection. Therefore, the regimens described in section 8.3.1 may also be used in patients with extrapulmonary tuberculosis, with some exceptions. Treatment of skeletal, miliary, and CNS tuberculosis requires daily administration of isoniazid, rifampin, pyrazinamide, and streptomycin for 1–2 months, followed by isoniazid and rifampin daily or twice weekly for another 10 months. The reason for the longer duration of treatment in the aforementioned cases is the limited number of controlled trials and hence experience with these agents in patients with extrapulmonary disease.

Diagnostic and/or therapeutic surgery (including total excision, incision and drainage, and wide debridement) may be indicated for extrathoracic tuberculous lymphadenitis. Ventriculoperitoneal shunting for CSF relief in tuberculous meningitis has also been reported. In the case of bone and joint disease, evacuation of large abscesses or even radical surgical reconstruction is sometimes required.

8.3.3 Drug-Resistant Tuberculosis

Primary drug resistance arises when a patient is infected with a strain of *M. tuberculosis* that is already resistant to a specific drug. Secondary resistance is the result of non-adherence of the patient to therapy or of the prescription of an inadequate treatment regimen by the doctor, either of which may lead to predominance of drug-resistant organisms within a given population of bacilli. If the adult source of an infected infant has been previously treated for tuberculosis, is seropositive for HIV infection, or lives in a community with high rates of primary drug resistance or HIV prevalence, it is very possible that the child will have drug-resistant tuberculosis.

According to the Working Group On Anti-Tuberculosis Drug Resistance Surveillance, between 1994 and 1997, median resistance to any single drug, isoniazid, rifampin, ethambutol, and multiple drugs was present in 9.9%, 7.3%, 1.8%, 1%, and 1.4% of patients, respectively, among patients from 35 countries with no prior treatment. Among patients who had received therapy in the past for <1 month, resistance to any of these drugs occurred in 36%, while multidrug resistance occurred in a median of 13% (range 0–54%). The highest rates of multidrug resistance were present in the former Soviet Union, Asia, the Dominican Republic, and Argentina. The impact of these data on childhood tuberculosis is obvious when one considers that contagious adults represent the only source for transmitting the disease to children.

When drug-resistant strains of *M. tuberculosis* are suspected, a regimen of isoniazid, rifampin, and pyrazinamide plus either streptomycin or ethambutol should be initially prescribed, pending the results of susceptibility tests. When the latter become available, treatment should include at least two bactericidal drugs to which the isolate is susceptible. Additionally, therapy should usually be continued for 12–18 months under directly observed therapy, in order to be effective and prevent further emergence of resistance.

8.3.4 Indications for the Use of Corticosteroids

Corticosteroids are indicated in select forms of tuberculous disease. Infants with serositis (pleural, pericardial effusion) experience significant symptomatic relief upon administration of corticosteroids. Patients with endobronchial tuberculosis with accompanying obstruction, emphysema, or atelectasis may also benefit from adjuvant corticosteroids. Tuberculous meningitis is a form of the disease with severe consequences and long-term neurologic sequelae, which may be partly alleviated by the use of corticosteroids. These drugs act by minimizing local inflammation and thus decreasing intracranial pressure. Corticosteroids are also indicated for miliary disease with alveolocapillary
block. Prednisone 1–2 mg/kg/day for 4–8 weeks with gradual tapering is the recommended regimen. Alternatively, dexamethasone 0.5 mg/kg/day may be prescribed.

8.3.5 Co-Infection with HIV

All children with tuberculous disease should be tested for HIV infection. HIV-seropositive infants with pulmonary tuberculosis should receive isoniazid, rifampin, pyrazinamide, and ethambutol or an aminoglycoside for 2 months, followed by isoniazid and rifampin for a total of at least 12 months. The fourth drug during the initial phase of treatment may be withdrawn if the isolated strain proves to be fully susceptible and disseminated forms of the disease are excluded. Meticulous monitoring is required in this subgroup of patients because of the increased frequency of drug resistance and adverse drug reactions as well as interactions with antiretroviral agents.

9. Prevention

Contacts of infectious adults with tuberculosis should be skin tested and appropriately managed. Infants in particular should receive the highest priority during investigation of contacts since their risk of progression to active disease once infected is very high.

BCG is the only vaccine available, to date, for the prevention of tuberculosis. According to WHO recommendations, BCG vaccines should be administered as a single dose during infancy, usually while the baby is in the maternity hospital. However, different countries have adopted diverse strategies regarding tuberculosis control. In most countries, BCG vaccination is administered as recommended by the WHO. However, in some countries it is recommended as a single dose administered at other ages (in Greece it is recommended at the age of 5–6 years), in the US BCG is not recommended in the routine vaccination schedule, and in other regions of the world it is recommended that the vaccine be administered twice.

Regarding the efficacy of the BCG vaccine in infants, various studies have been conducted with different results produced. Protection seems to be higher for disseminated forms of the disease than for pulmonary tuberculosis, and the effect is probably time limited since vaccination during infancy does not decrease the incidence of tuberculosis in adults. However, the BCG vaccination is recommended for Mantoux skin test-negative infants and young children who are inevitably exposed to under-treated infectious adults or sources with multidrug-resistant disease. The BCG vaccine is considered extremely safe with the most common adverse effects consisting of a local ulceration and regional suppurative adenitis; osteitis and systemic complaints (fever, irritability etc.) occur with a much lower frequency.

It is worth mentioning, as a reflection of the magnitude of ongoing research regarding tuberculosis prevention, that as of June 2001, more than 190 candidate vaccines had been screened in animal models.

10. Conclusions

Tuberculosis in infants, whether congenital or postnatally acquired, necessitates timely diagnosis and appropriate management of both the patient and contacts. The disease process is rapidly evolving in this immunologically immature age group and the outcome may be fatal if a high index of suspicion is not maintained. As shorter and more effective therapeutic regimens are designed and clinically established, physicians should be able to encompass latest guidelines and recommendations in their everyday practice. Finally, further studies focused on the infantile patient are needed, in order to achieve optimal conventional or alternative therapy for the prevention and treatment of tuberculosis.

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Correspondence and offprints: Dr Dimitrios A. Kafetzis, Second Department of Pediatrics, 'P. and A. Kiriakou' Children's Hospital, University of Athens, Thيون and Livadias st., Athens, GR-11527, Greece. E-mail: kafetzis@ath.forthnet.gr

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