# SUPPLEMENTARY ON-LINE MATERIAL

**Supplementary Table 1**. Differential diagnosis of chronic cough in children

| Cause | Nature of Cough | Associated Features | Response to Therapy |
|---|---|---|---|
| **Infectious diseases** | | | |
| **Pulmonary tuberculosis** | Wet, persistent & unremitting cough. Mucopurulent sputum; rarely bloody (with underlying bronchiectasis or cavitary disease). | Variable fever. Failure to thrive / malnutrition. Exposure to TB; fatigue or decreased activity/playfulness; mediastinal, hilar lymphadenopathies. | Not resolved with trial of antibiotics. Significant improvement with TB treatment |
| **Lymph node tuberculosis** | Dry, persistent & unremitting cough. | Variable fever. Failure to thrive / malnutrition. Subacute onset; wheezing or stridor. | No response to bronchodilators or antibiotics; Significant improvement with TB treatment |
| **Recurrent viral respiratory tract infection** | Acute-onset cough, initially dry then wet | Recurrent fever. Normal nutritional status. Especially infants; coryza, sore throat; improvement between episodes. | Delayed recovery, with back-to-back relapses; no response to antibacterials. |
| **Bronchiolitis** | Cough marked at onset, with steady improvement. | Fever at onset, then resolves. Normal nutritional status. Wheezing; infants. | Responsive to general supportive measures. |
| **Pertussis-like syndrome** (e.g., *Bordetella*; *Chlamydophila*; *Mycoplasma*; resp. viruses) | Intractable, loud, dry, paroxysmal cough; not always with inspiratory whoop. Small amounts of viscid clear sputum. | Fever at onset, then resolves. Normal nutritional status. Not immunized; subconjunctival hemorrhages. | Can be very slow to resolve, antibiotics have limited impact |
| **Protracted bacterial bronchitis** (e.g., *S. pneumoniae*;<br>*H. influenzae*; *M. catarrhalis*) | Persistent wet-moist cough with delayed recovery. Mucopurulent sputum. | Fever at onset, then resolves. Normal nutritional status. Especially young children (< 5 y.o.), who otherwise appear well. | Resolves with prolonged (>2-weeks) oral antibiotics |
| **Recurrent bacterial pneumonia** | Acute-onset cough, then improvement, then relapse. Mucopurulent sputum. | Recurrent fever. Failure to thrive / malnutrition. Improvement between episodes; may be HIV-related. | Resolves with antibiotics |
| **Chronic bacterial rhinosinusitis** | Persistent cough, worse when lying down. | Fever at onset, then resolves. Normal nutritional status. Postnasal drainage. | Resolves with appropriate treatment |
| **Allergic disease** | | | |
| **Allergic chronic** | Variable cough, worse | Fever absent unless assoc. with | Can be controlled with |

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| **rhinosinusitis** | when lying down. | secondary infection. Normal nutritional status. Nasal congestion & postnasal drainage; frequent clearing of throat. | ongoing combination of allergen avoidance, medications, immunotherapy. |
| **Cough-dominant asthma** | Recurrent episodes of cough, usually dry, worse at night. May be productive of thick/mucoid sputum. | Fever absent unless assoc. with secondary infection. Normal nutritional status. May be accompanied by wheezing & dyspnea. | Responsive to bronchodilators & glucocorticoids |
| **Mucociliary disorders** | | | |
| **Cystic fibrosis** | Persistent wet cough. Copious viscid mucopurulent sputum. | Variable fever. Failure to thrive / malnutrition. Begins in early childhood; bronchiectasis; frequent wheezing; clubbing; generally Caucasian. | Acute exacerbations resolve with antibiotics; chronic cough ameliorated with daily pulmonary hygiene therapies. |
| **Primary ciliary dyskinesia** | Persistent moist cough. Mucoid or purulent sputum. | Fever absent (even sometimes during exacerbations). Normal nutritional status. Bronchiectasis; occasional wheezing; chronic rhinosinusitis, recurrent otitis media; may have situs inversus. | Acute exacerbations resolve with antibiotics; chronic cough ameliorated with daily pulmonary hygiene therapies. |
| **Aspiration syndromes** | | | |
| **Gastroesophageal reflux disease** (GERD) | Dry cough with variable persistence, worse at night, sometimes associated with stridor and wheezing; hoarseness. | Fever absent unless assoc. with aspiration-related lower respiratory tract infection. Failure to thrive (especially in severe cases). Children with neurologic abnormalities are at greater risk for aspiration complications (pneumonitis/pneumonia). | Usually responsive to dietary and medical measures.<br>Dysphagia cases may be responsive to swallow therapy; |
| **Retained foreign body** | Persistent cough. | Fever absent unless assoc. with secondary infection. Normal nutritional status. Especially toddlers; choking episode at onset of aspiration. | Removal of aspirated foreign body by rigid bronchoscopy. |
| **Others** | | | |
| **Lymphoid interstitial pneumonitis (LIP)** | Persistent cough. | Variable fever. Variable nutritional status. HIV-infected; parotid enlargement; persistent generalized lymphadenopathy; clubbing. | Responsive to corticosteroids. |

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| **Tracheomalacia (TM)** | Brassy cough, expiratory stridor, wheezing. Thin, clear, scarce sputum. | Fever absent unless assoc. with secondary infection. Normal nutritional status. Laryngeal clefts, tracheoesophageal fistula, bronchomalacia. | Mild congenital TM improves as the infant grows. Severe TM requires surgical care. |
| **Congestive heart failure** | Persistent cough; worse at night. Thin, frothy sputum. | Fever absent unless assoc. with secondary infection. Failure to thrive / malnutrition. Pulm. edema; exercise intolerance & easy fatigue; respiratory distress with tachypnea; hepatomegaly. | Depends on the underlying etiology. |

**LIP**: lymphoid interstitial pneumonitis; **TB**: tuberculosis; **TM**: tracheomalacia

Adapted from C.M. Perez-Velez. Diagnosis of Intrathoracic Tuberculosis in Children. In: Handbook of Child and Adolescent Tuberculosis (p. 162-165), J.R. Starke and P.R. Donald (Eds.), 2016, New York, NY: Oxford University Press. Copyright by Oxford University Press [15]. Adapted with permission.

**Supplementary Table 2**. Nucleic acid amplification tests for detecting *Mycobacterium tuberculosis* complex and genes encoding targets of mutations conferring drug resistance

| **NAAT** | **Type** | **Gene Encoding Target** | **Drug-Resistance: Gene Encoding Target of Mutations** | **Analytical Sensitivity (Limit of Detection)** (CFU/mL) | **Recommended Smear Status for Detecting *M. tb*** | **Turnaround Time** | **Required Risk Level of Laboratory** | **Year of Release** | **Endorsement/ Approval** |
|---|---|---|---|---|---|---|---|---|---|
| **GenoType MTBDR*plus*** version 2 (Hain Lifescience) | Line probe assay | - *M. tb* complex: 23SrRNA | - Rmp: *rpoB*<br>- INH: *katG*; *inhA* | 1000-10,000 | Only positive | 4-6 hours (manual) | High | 2012 (version 1 in 2004) | WHO |
| **GenoType MTBDR*sl*** | Line probe | - *M. tb* complex: 23SrRNA | - Fluoroquinolones: | 1000-10,000 | Only positive | 4-6 hours (manual) | High | 2012 (version 1 | WHO |

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| version 2<br>(Hain Lifescience) | assay | | *gyrA*<br>- Aminoglycosides &<br>Cyclic Peptides: *rrs*<br>- Emb: *embB* | | | | | in 2009) | |
| **Genoscholar**<br>**NTM + MDRTB**<br>(Nipro) | Line probe assay | - *M. tb* complex<br>- *M. avium*<br>- *M. intracellulare*<br>- *M. kansasii* | - Rmp: *rpoB*<br>- INH: *katG*; *inhA* | 1000-10,000 | Only positive | 4-6 hours<br>(manual) | High | 2012 | WHO |
| **COBAS TaqMan MTD Test (Roche)** | RT-PCR | - *M. tb* complex: 16S rRNA | N/A | 20 | Only positive | 6.5 hours<br>(automated) | Moderate | 2010 | FDA |
| **Xpert MTB/RIF**<br>(Cepheid) | RT-PCR | - *M. tb* complex: *rpoB* | - Rmp: *rpoB* | 100-150 | Positive &<br>Negative | 1-2 hours<br>(automated) | Low | 2010 | WHO<br>FDA |
| **Xpert MTB/RIF Ultra**<br>(Cepheid) | RT-PCR | - *M. tb* complex: *rpoB* | - Rmp: *rpoB* | 10-100 | Positive &<br>Negative | 1-2 hours<br>(automated) | Low | ? 2017 | N/A |

**CFU**: colony-forming units; **Emb**: ethambutol; **FDA**: Federal Drug Agency; **INH**: isoniazid; ***M. tuberculosis****:* *Mycobacterium tuberculosis*; **NAAT**: nucleic acid amplification test; **RT-PCR**: real-time polymerase chain reaction; **TAM**: transcription-mediated amplification; **WHO**: World Health Organization.

**Supplementary Table 3**: Differential diagnosis of clinical-radiological syndromes associated with intrathoracic TB in children

| **Clinical-Radiological Syndrome** | **Differential Diagnosis** | |
|---|---|---|
| | **Infectious** | **Non-Infectious** |

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| **Lymph Node Disease** |  |  |
| Lymphadenopathies,<br>Mediastinal/Hilar/Paratracheal<br>- Noncalcified<br>- Calcified (Ranke) | Mycobacteria: *M. tb*; MAC<br>Fungi: *Histoplasma*; *Coccidioides*<br>Bacteria: *B. pertussis*, *B. henselae* (cat scratch disease)<br>Viruses: HIV; measles<br>Parasite: *Toxoplasma* | Tumors: lymphoma (Hodgkin's & non-Hodgkin's); lymphangioma; lymphosarcoma; leukemia<br>Others: sarcoidosis; hyperplastic thymus (or even normal thymus in infant); teratoma |
| **Parenchymal Lung Disease** |  |  |
| Solitary pulmonary nodule<br>- Noncalcified<br>- Calcified | Mycobacteria: *M. tb* (primary Ghon focus); MAC<br>Fungi: *Histoplasma*; *Aspergillus*; *Coccidioides* | Malignant tumors: sarcoma; lymphoma germ cell tumor<br>Others: hamartoma; arteriovenous malformations |
| Multiple focal pulmonary nodules<br>- Noncalcified<br>- Calcified | Mycobacteria: *M. tb*; MAC<br>Bacteria: septic pulmonary emboli due to *S. aureus*; *Nocardia*<br>Atypical Bacteria: *M. pneumoniae*; *Legionella; C. psittaci*<br>Fungi: *Aspergillus*; *Cryptococcus*; *Histoplasma*; Coccidioides; *Candida*<br>Viruses: CMV; VZV; HSV; HPV | Malignant tumors: sarcoma; lymphoma; Wilms' tumor<br>Autoimmune: granulomatosis with polyangiitis (Wegener's)<br>Others: hamartoma; recurrent pulmonary aspirations; hypersensitivity pneumonitis; pulmonary hemosiderosis |
| Diffuse pulmonary micronodules | Bacteria: streptococci & *Listeria* (esp. neonates)<br>Mycobacteria: *M. tb* (miliary disease)<br>Fungi: *Aspergillus*; *Cryptococcus*; *Histoplasma*; *Coccidioides*; mucormycosis | Malignant tumors: sarcoma<br>Benign tumors: inflammatory myofibroblastic tumor<br>Others: toxic fume inhalation; alveolar hemorrhage syndrome |
| Pneumonia |  |  |
| Acute lobar pneumonia | Viruses: RSV; influenza; parainfluenza; adenovirus; metapneumovirus<br>Bacteria: *S. pneumoniae*; *S. aureus*; *S. pyogenes*; *H. influenzae*; *K. pneumoniae* | Congenital malformations: bronchopulmonary sequestration; bronchogenic cyst; tracheoesophageal fistula<br>Others: pulmonary infarct |

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| | Mycobacteria: *M. tb* | |
| Subacute lobar pneumonia | Atypical Bacteria: *M. pneumoniae*, *C. pneumoniae*<br>Viruses: adenovirus<br>Mycobacteria: *M. tb*; MAC; *M. abscessus* | Aspiration syndromes: aspiration pneumonia |
| Chronic lobar pneumonia | Bacteria: *Actinomyces*; *B. anthracis*; anaerobes<br>Atypical Bacteria: *M. pneumoniae*; *C. pneumoniae*; *F. tularensis*<br>Mycobacteria: *M. tb*; MAC; *M. abscessus*<br>Fungi: *Histoplasma*; *Coccidioides*; *Blastomyces*; *Cryptococcus*<br>Parasites: *Paragonimus* | Aspiration syndromes: aspiration pneumonia; foreign body |
| Cavitary pulmonary disease<br>- Solitary cavity<br>- Multiple cavities | Bacteria: *S. aureus*; *K. pneumoniae*; *Actinomyces*; *Nocardia*; anaerobes<br>Mycobacteria: *M. tb* (progressive Ghon focus)<br>Fungi: *Histoplasma*; *Coccidioides*; *Aspergillus*; *Pneumocystis*<br>Viruses: HPV; influenza; measles<br>Parasites: *Paragonimus*; *E. histolytica*; *Echinococcus* | Malignant tumors: lymphoma<br>Benign tumors: inflammatory pseudotumor<br>Autoimmune: granulomatosis with polyangiitis (Wegener's)<br>Others: cystic bronchiectasis; congenital; sarcoidosis; traumatic pneumatocele |
| **Airway Disease** | | |
| Subacute/Chronic bronchitis | Virus: post-viral reactive airways disease<br>Atypical Bacteria: *M. pneumoniae*; *C. pneumoniae*<br>Bacteria: protracted bacterial bronchitis (*H. influenzae; S. pneumoniae*; *M. catarrhalis)*<br>Mycobacteria: *M. tb*<br>Fungi: *Aspergillus* (e.g., ABPA) | Obstructive airway diseases: asthma; cystic fibrosis<br>Others: bronchomalacia; gastroesophageal reflux; airway irritation by smoke or air pollution |
| Endobronchial granulomas | Mycobacteria: *M. tb*; MAC | Autoimmune: eosinophilic granulomatosis |

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|---|---|---|
| | Viruses: HPV | with polyangiitis<br>Others: sarcoidosis |
| Tree-in-bud pattern | Mycobacteria: *M. tb*; MAC<br>Fungi: *Aspergillus*; *Pneumocystis*<br>Viruses: RSV; parainfluenza | Mucociliary disorders: cystic fibrosis; primary ciliary dyskinesia<br>Autoimmune: rheumatoid arthritis |
| Bronchiectasis | Sequelae of chronic/severe airway infections due to the following:<br>Bacteria: *S. aureus*; *K. pneumoniae*; *B. pertussis*<br>Mycobacteria: *M. tb*; MAC<br>Viruses*:* influenza; RSV; adenovirus; measles<br>Fungi: *Aspergillus* | Mucociliary disorders: cystic fibrosis; primary ciliary dyskinesia<br>Aspiration syndromes: recurrent pulmonary aspiration; foreign body |
| **Pleural Disease** | | |
| Pleural effusion | Bacteria: *S. pneumoniae*; *S. aureus*; *H. influenzae*; *P. aeruginosa*; *Actinomyces*<br>Atypical Bacteria: *M. pneumoniae*<br>Virus: adenovirus; influenza<br>Mycobacteria: *M. tb*<br>Fungi: *Aspergillus*; *Histoplasma*<br>Parasite: *Paragonimus* | Malignant tumors: lymphoma<br>Autoimmune: systemic lupus erythematosus<br>Vascular: lymphatic disorders |
| Chylothorax | Mycobacteria: *M. tb* (mediastinal lymph node disease)<br>Fungi: *Histoplasma* (mediastinal lymph node disease) | Malignant tumors: lymphoma; teratoma; sarcoma; neuroblastoma<br>Others: thoracic duct injury; congenital malformation; sarcoidosis |

**ABPA**: allergic bronchopulmonary aspergillosis; ***B. anthracis****: Bacillus anthracis;* ***B. henselae:*** *Bartonella henselae;* ***B. pertussis****: Bordetella pertussis;* **CMV**: cytomegalovirus; ***C. pneumoniae***: *Chlamydophila pneumoniae*; ***C. psittaci***: *Chlamydia psittaci*; ***E. histolytica***: *Entamoeba histolytica*; ***F. tularensis***: *Francisella tularensis*; ***H. influenzae***: *Haemophilus influenzae;* **HIV**: human immunodeficiency virus; **HPV**: human papillomavirus; **HSV**: herpes simplex virus; ***K. pneumoniae***: *Klebsiella pneumoniae*; ***M. abscessus***: *Mycobacterium abscessus*; ***M. catarrhalis***: *Moraxella catarrhalis*; ***M. pneumoniae***: *Mycoplasma pneumoniae*; ***M. tb:*** *Mycobacterium tuberculosis*; **MAC**: Mycobacterium avium complex; ***P. aeruginosa***: *Pseudomonas aeruginosa*; **RSV**: respiratory syncytial virus; ***S. aureus***: *Staphylococcus aureus*; ***S. pneumonia***: *Streptococcus pneumonia*; ***S. pyogenes***: *Streptococcus pyogenes*; **VZV**: varicella zoster virus

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**Supplementary Textbox 1**. Spectrum of possible organ involvement in TB disease

- **Respiratory System** (including chest): lungs; pleura; larynx; nasopharynx; sinuses.
- **Reticuloendothelial System**: lymph nodes; bone marrow; liver; spleen.
- **Cardiovascular System**: pericardium; myocardium.
- **Central Nervous System** (including head, neck, ears, and eyes): meninges; brain; orbit; optic neuritis; retina; uvea; sclera; conjunctiva.
- **Musculoskeletal System**: bone; joint; bursa; muscle.
- **Urinary System**: kidneys; ureters; bladder.
- **Alimentary/Digestive System** (including abdomen): oral cavity; esophagus; intestine; peritoneum; liver; gallbladder.
- **Endocrine System**: pancreatic; adrenal; thyroid; parathyroid; breast; pituitary; testicular; ovarian.
- **Reproductive/Genital System**: uterine; oviduct; vulva; prostate; epididymis; penis.
- **Integumentary System**: skin.

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**Supplementary Textbox 2**. Risk factors for TB infection in children

**Close contact with an adult or adolescent with confirmed or suspected pulmonary TB**

**Close contact with an adult or adolescent known to have TB infection**

**Having one of the following risk factors for TB infection, or having a close contact with an adult or adolescent having one of them**:

- Birth in, or travel to, an area of the world that is endemic for TB (especially during the last five years)
- Residing or working with persons who are at high risk for TB in a congregate setting such as a:
  - healthcare institution that cares for high-risk patients (if infection control is not adequate), including:
    - general and psychiatric hospitals and clinics
    - urgent care centre
    - physician's office
    - skilled nursing facility
  - long-term residential facilities

    - correctional institution
    - homeless shelter
- Homelessness
- Illicit drug use, particularly by injection