Diagnosis of community-acquired pneumonia in children: South African Thoracic Society guidelines (part 2)

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Background. Accurate diagnosis and attribution of the aetiology of pneumonia are important for measuring the burden of disease, implementing appropriate treatment strategies and developing more effective interventions.
Objectives. To produce revised guidelines for the diagnosis of pneumonia in South African (SA) children, encompassing clinical, radiological and aetiological methods.
Methods. An expert group was established to review diagnostic evidence and make recommendations for a revised SA guideline. Published evidence was reviewed and graded using the British Thoracic Society grading system.
Results. Diagnosis of pneumonia should be considered in a child with acute cough, fast breathing or difficulty breathing. Revised World Health Organization guidelines classify such children into: (*i*) severe pneumonia; (*ii*) pneumonia (tachypoea or lower chest indrawing); or (*iii*) no pneumonia. Malnourished or immunocompromised children with lower chest indrawing should be managed as cases of severe pneumonia. Pulse oximetry should be done, with hospital referral for oxygen saturation <92%. A chest X-ray is indicated in severe pneumonia or when tuberculosis (TB) is suspected. Microbiological investigations are recommended in hospitalised patients or in outbreak settings. Improved aetiological methods show the importance of co-infections. Blood cultures have a low sensitivity (<5%), for diagnosing bacterial pneumonia. Highly sensitive, multiplex tests on upper respiratory samples or sputum detect multiple potential pathogens in most children. However, even in symptomatic children, it may be impossible to distinguish colonising from causative organisms, unless identification of the organism is strongly associated with attribution to causality, e.g. respiratory syncytial virus, *Mycobacterium tuberculosis*, *Bordetella pertussis*, influenza, para-influenza or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Investigations for TB should be considered in children with severe pneumonia who have been hospitalised, in a case of a known TB contact, if the tuberculin skin test is positive, if a child is malnourished or has lost weight, and in children living with HIV. Induced sputum may provide a higher yield than upper respiratory sampling for *B. pertussis, M. tuberculosis* and *Pneumocystis jirovecii.*
Conclusions. Advances in clinical, radiological and aetiological methods have improved the diagnosis of childhood pneumonia.

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Diagnosis of pneumonia should be considered in any child with acute respiratory symptoms, including cough, fast breathing or difficulty breathing. Diagnostic modalities include clinical, radiographic and aetiological evaluation to: (*i*) establish whether pneumonia is present; (*ii*) assess severity of pneumonia; (*iii*) detect complications; and (*iv*) determine causative organism/s. In general, investigations to determine the cause of pneumonia are indicated only in children who require hospitalisation.

Clinical evaluation

The main symptoms of pneumonia are cough, difficulty breathing or tachypnoea. Physical examination should include: assessment of

the child's general appearance, measurement of respiratory rate, evaluation of the work of breathing and doing pulse oximetry. Auscultation of the chest should be done where possible (evidence level II); however, there is wide inter- and intra-observer variability in the interpretation of auscultatory sounds in paediatric pneumonia.[1]

The World Health Organization (WHO) guidelines classify children with cough or difficulty breathing into three categories, based on clinical signs – severe pneumonia, pneumonia or no pneumonia (evidence level Ia) (Fig. 1; Table 1).[2] Children with lower chest indrawing are now classified as having pneumonia, rather than severe pneumonia. Treatment is based on these categories – severe pneumonia requires referral to hospital and administering antibiotics; pneumonia requires oral antibiotics and outpatient management with follow-up; and no pneumonia is treated symptomatically. However, children living with HIV (CLWH), malnourished children or immunocompromised children who present with lower chest indrawing, should be regarded as having severe pneumonia and referred to hospital for appropriate management (evidence level Ib).

Assessment of severity

Assessment of the **general appearance** of the child is helpful to evaluate severity of illness. Any child with a general danger sign requires referral to hospital. All children <2 months of age with signs of pneumonia require hospital admission (Table 2).

Excessive **work of breathing,** as indicated by grunting, nasal flaring or very severe chest wall indrawing, is a useful indicator of severity (evidence level Ia).[3,4] British Thoracic Society (BTS) guidelines recommend that signs indicating excessive work of breathing are more specific for diagnosing severe pneumonia than respiratory rate (evidence level II).[5]

Assessment of **oxygenation** is important as a measure of severity (evidence level Ia).[6] Pulse oximetry should be performed in all children, using a paediatric wrap-around probe (evidence level Ib). A saturation of <92% or <90% at higher altitudes (≥1 800 m) indicates

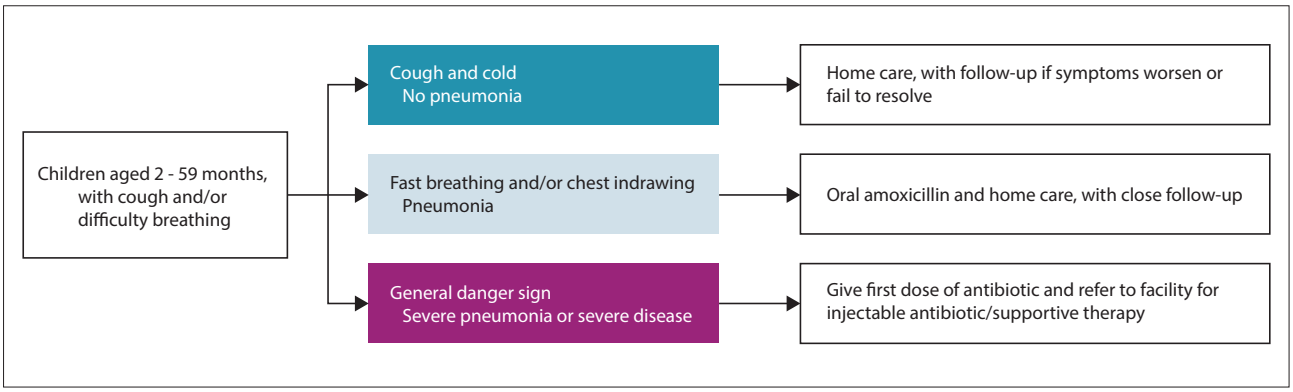

Fig. 1. Revised World Health Organization classification and treatment of childhood pneumonia at health facilities.[2]

Table 1. Categories of pneumonia – World Health Organization classification[2]

Category	Characteristics
Severe pneumonia	Any child with a general danger sign
	Inability to drink
	Convulsions
	Abnormal sleepiness
	Persistent vomiting
	or
	Oxygen saturation <90% (at altitude >1 800 m) or <92% or central cyanosis
	or
	Severe respiratory distress (grunting, very severe chest indrawing)
	Infant <2 months of age with
	A general danger sign
	or
	Chest wall indrawing
	or
	Tachypnoea (≥60 breaths per min)
	Children living with HIV, immune-compromised or malnourished children with
	Lower chest indrawing
Pneumonia	Child >2 months of age with
	Lower chest indrawing
	or
	Tachypnoea
	≥50 breaths per min for infants 2 - 11 months of age
	≥40 breaths per min for children 1 - 5 years of age
No pneumonia	No signs of pneumonia or severe pneumonia, i.e. upper respiratory tract infection

the need for hospital admission and supplemental oxygen (evidence level Ia).[5,7]

Radiological diagnosis

A chest X-ray (CXR) may be useful for confirming the presence of pneumonia or complications such as a lung abscess or empyema (Table 3). A CXR cannot accurately discriminate between viral and bacterial pneumonia (evidence level II).[5,7,8] Overall, undertaking a CXR does not influence outcome and rarely informs changes of treatment in the ambulatory setting (evidence level Ib).[8] There is also no evidence that a lateral CXR improves the diagnostic yield in children with pneumonia,[9] except for detection of hilar adenopathy if tuberculosis (TB) is suspected (evidence level II).[10,11]

The use of a CXR has several limitations, including radiographic features being masked by anatomical structures; a normal CXR in the early stages of pneumonia; and lack of inter-reader agreement in interpretation.[12] Clinician-led point-of-care ultrasound is increasingly being used, with higher inter-observer agreement than for a CXR (evidence level Ib).[12,13] Evidence suggests a similar or higher yield in the diagnosis of consolidation or pleural effusion when using ultrasound (evidence level Ib). However, ultrasound is not yet routinely available for the diagnosis of pneumonia, and a CXR remains the standard investigation.[12]

Computed tomography (CT) is not recommended as a first-line diagnostic tool, but where available, can be considered for detecting complications of pneumonia in the acute or subacute phase (for diagnosing a suppurative complication such as necrotising pneumonia, abscess or empyema) and in the chronic phase (for diagnosing bronchopleural fistula or detecting and localising bronchiectasis); it can also be useful for differentiating pneumonia from other pathological conditions, including endobronchial lesions/foreign bodies causing atelectasis and for demonstrating previously undiagnosed, underlying congenital lesions.[5,7] Radiation dose is less of a concern, as low-dose scans (at doses of ~10 CXRs or 3 - 5 antero-posterior and lateral CXRs) can be performed.

Follow-up chest X-ray

A follow-up CXR after acute uncomplicated pneumonia is not indicated if there is clinical improvement (evidence level II).[7,16] A follow-up CXR at 2 - 4 weeks should be done: (*i*) in children with lobar collapse; (*ii*) to document resolution of a round pneumonia (as this may mimic the appearance of a Ghon focus); and (*iii*) in those with ongoing respiratory symptoms.[5,7] A chest ultrasound scan should be considered as an alternative to a repeat CXR in children with unresolving or worsening signs and symptoms to detect complications such as pleural effusion (evidence level Ib).[13,17,18]

Table 2. Indications for hospital admission

All children <2 months of age
Children >2 months of age with
A general danger sign
Grunting, severe lower chest indrawing
Stridor in a calm child
Room air arterial oxygen saturation <92% at sea level or <90% at high altitude, or central cyanosis
Severe malnutrition
HIV-infected, immune-compromised or malnourished child with lower chest indrawing
Family unable to provide appropriate care

Aetiological diagnosis

Clinical assessment and chest radiography cannot determine the aetiology of pneumonia.[5,19-21] Diffuse bilateral wheezing is, however, often associated with a viral infection, especially respiratory syncytial virus (RSV) (evidence level Ib).[20] Various diagnostic modalities are available for aetiological diagnosis, such as microscopy, molecular diagnostics, culture and antigen detection (Table 4). Recent advances in understanding the aetiology have highlighted that pneumonia may be due to interactions or co-infection with several organisms, including viral-viral and viral-bacterial infections.[7,22] Testing of upper respiratory samples may not, however, discriminate between colonising and pathogenic organisms, making it difficult to attribute aetiology. Identification of organisms such as *Bordetella pertussis*, RSV, influenza virus, para-influenza virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or *Mycobacterium tuberculosis* in upper respiratory samples among symptomatic children is, however, strongly attributable to the aetiology of lower respiratory tract infection (evidence level Ia).[23,24]

The following should be considered when investigating the aetiology:

- General tests for infection, including acute-phase reactants (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white cell count (WCC), neutrophil count and procalcitonin (PCT)) do not reliably differentiate bacterial from viral pneumonia and should not be routinely used (evidence level Ib).[7,25] CRP concentrations ≥40 mg/L with radiological confirmation of pneumonia may suggest bacterial pneumonia (evidence level II).[26]
- HIV status should be determined in all children requiring hospital admission for pneumonia.
- Microbiological investigations on blood, pleural fluid or respiratory samples should only be done in children requiring hospital admission, i.e. in those with severe disease or complications, or in outbreak situations (evidence level IVa).[5,7]
- For detection of viruses, polymerase chain reaction (PCR) and/or immunofluorescence on nasal samples may be useful (evidence level Ib). Viruses strongly associated with pneumonia include RSV, influenza and para-influenza virus. Detection of adenovirus, human metapneumovirus (HMPV) or rhinovirus, even though associated with pneumonia, should be interpreted with caution, as healthy children or those with upper respiratory tract infection may have a positive test (evidence level Ia).[22,27] Testing for SARS-CoV-2 using PCR can be done on mid-turbinate nasal swabs.
- Blood culture has a very low diagnostic yield. Antibiotic pre-exposure and specimen volume impact on blood culture yield.[28] Overall, ~5% of blood cultures of suspected bacterial pneumonia

Table 3. Indications for chest X-ray (evidence level Ib)

- Severe pneumonia
- Suspected pulmonary tuberculosis
- Suspected foreign body aspiration
- Pneumonia unresponsive to standard management
- Consider in children <5 years of age, presenting with fever (>39°C), leukocytosis and no obvious source of infection, as ~18% of such patients have radiographic pneumonia (evidence level III)[14,15]

Table 4. Summary of investigations in children hospitalised for pneumonia[12]

	Advantages	Disadvantages
Vital signs		
Pulse oximetry	Accurate measure of hypoxaemia; guides the use of supplemental oxygen	-
Radiological tests		
Chest X-ray	Assess extent of pneumonia Detect complications	Unable to distinguish aetiology Poor intra- and inter-observer agreement for interpretation of some features
Lung ultrasound	Higher inter- and intrapersonal agreement of radiological findings compared with CXR May be more sensitive than CXR for detecting abnormalities Easily repeatable, no radiation Can be done by non-radiologists with minimal training	Not widely available Few clinicians have expertise in its use
Blood		
Culture for bacterial pathogens	Relative ease of collection Positive culture with a clinically significant pathogen has high specificity Able to guide empirical antibiotic susceptibility patterns	Low sensitivity; therefore, high cost per case detected
Molecular testing	More sensitive than blood culture for some targets, e.g. pneumococcal *lytA* Useful for CMV viral load	Lacks specificity for disease, e.g. *lytA* detection may reflect pneumococcal carriage
Serology	Useful for epidemiological studies and for specific pathogens, e.g. *B. pertussis*	Usually requires acute and convalescent sera; therefore, not useful for guiding acute treatment decisions
Biomarker detection	Potential to discriminate bacterial v. viral infection	Accuracy for distinguishing bacterial v. viral pneumonia is suboptimal for available biomarkers (CRP, ESR and PCT)
HIV infection	HIV testing essential in hospitalised children whose HIV status is unknown HIV infection or HIV exposure may impact on the spectrum of pathogens considered in empirical antibiotic therapy	-
Nasopharyngeal or nasal swab or aspirate		
Bacterial culture, molecular or antigen detection of bacteria and viruses	Ease of collection, relatively good correlation of results with sputum testing, method of choice for some viruses (e.g. RSV, influenza, para-influenza virus, SARS-CoV-2), bacteria (*B. pertussis*) and *P. jirovecii*	Colonisation or infection of the upper airway does not imply that organisms are causing pneumonia Predictive value of attributing causality is high for RSV, influenza virus, para-influenza virus 3 and *M. tuberculosis* Limited value for most other bacteria and viruses
Sputum (expectorated or induced)		
Bacterial culture, molecular or antigen detection of bacteria (*M. tuberculosis, B. pertussis*) or *P. jirovecii*	Relative ease of collection Incremental yield over testing of upper respiratory samples for *M. tuberculosis, B. pertussis* and *P. jirovecii*	Requires expertise, and should be conducted in a dedicated space that is well ventilated May also detect organisms colonising or infecting upper airway
Urine antigen testing		
Antigen detection	Relative ease of collection	Poor specificity for pneumococcal disease in children due to high prevalence of nasopharyngeal carriage

Continued ...

Table 4. (continued) Summary of investigations in children hospitalised for pneumonia[12]

	Advantages	Disadvantages
Tracheal aspiration or bronchoalveolar lavage		
Bacterial culture, molecular or antigen detection of bacteria, *P. jirovecii* and viruses	More representative of organisms in the lower respiratory tract Less likely to be contaminated by upper respiratory tract flora	Few comparative studies v. other sample types Costly, invasive, requires expertise and patient intubation
Percutaneous lung aspiration		
Bacterial culture, molecular or antigen detection of bacteria and viruses	Most representative of lower respiratory tract, least contamination with upper airway respiratory tract flora	Useful mainly for peripheral infective foci in the right lung Invasive, and requires expertise Small risk of serious complications

CXR = chest X-ray; CMV = cytomegalovirus; *B. pertussis = Bordetella pertussis;* CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PCT = procalcitonin; RSV = respiratory syncytial virus; *P. jirovecii = Pneumocystis jirovecii; M. tuberculosis = Mycobacterium tuberculosis.*

cases are positive; the yield is higher in severe pneumonia[29,30] and in CLWH.[31]

- Induced sputum may provide a higher yield than upper respiratory secretions for *B. pertussis, Pneumocystis jirovecii* and *M. tuberculosis*.[32-36]
- Pulmonary TB should be considered in a child presenting with pneumonia or severe pneumonia, in a case of a known TB contact, if the tuberculin skin test is positive, if the child is malnourished or has lost weight, and in CLWH or in those who are HIV-exposed (evidence level 1b).[37-39] Two sequential respiratory samples, preferably expectorated or induced sputum, should be tested with Xpert MTB/RIF Ultra (Cepheid, USA) and mycobacterial culture (evidence level Ib).[40]
- Pleural fluid can be tested for microscopy, culture, pneumococcal antigen (by latex agglutination), PCR for bacteria, mycobacterial culture and Xpert MTB/RIF Ultra (evidence level II).

Summary: Diagnosis

1. A diagnosis of pneumonia should be considered in any child who has an acute onset of cough, fast breathing or difficulty breathing.
2. Revised WHO guidelines classify children with cough or difficulty breathing into: (*i*) severe pneumonia; (*ii*) pneumonia; and (*iii*) no pneumonia. Malnourished or immunocompromised children with lower chest indrawing should be managed as severe pneumonia (evidence level Ib).
3. Excessive work of breathing, as indicated by grunting, nasal flaring or severe chest wall indrawing, is an important indicator of severity (evidence level Ia).
4. Pulse oximetry should be performed on all children, with referral to hospital for oxygen if saturation is <92% or <90% at an altitude >1 800 m (evidence level Ia).
5. A CXR should not be done routinely (evidence level Ib), but should be performed in severe cases to confirm pneumonia and detect complications or when TB is suspected.
6. A follow-up CXR should only be done if the condition of a child does not improve or complications are suspected (evidence level II).
7. Evidence for point-of-care chest ultrasound for diagnosis is accumulating. A chest ultrasound scan, rather than a repeat CXR, should be considered in children with ongoing symptoms (evidence level II).
8. CRP ≥40 mg/L with radiological confirmation of pneumonia is supportive of a bacterial aetiology (evidence level II).
9. Microbiological investigations should not be performed routinely on children, but only in those requiring hospitalisation or in outbreak settings (evidence level IVa).
10. Testing of nasal samples with PCR is useful for detecting RSV, influenza virus, para-influenza virus or SARS-CoV-2; other viruses should be cautiously interpreted, as healthy children or those with upper respiratory tract infection may have a positive test.
11. Induced sputum may provide a higher yield than upper respiratory samples for *B. pertussis, P. jirovecii* and *M. tuberculosis.*
12. Investigations for TB should be done in children with pneumonia or severe pneumonia, a history of a TB contact, a positive tuberculin skin test, loss of weight or malnutrition or if HIV-infected.

Impact of HIV infection on clinical diagnosis of pneumonia

Clinical signs of pneumonia are similar in CLWH and HIV-uninfected children; however, CLWH who are not on antiretroviral therapy (ART) are more likely to present with severe disease and have higher rates of treatment failure than immune-competent children (evidence level Ib).[41,42] Pneumonia resulting from opportunistic pathogens, such as *P. jirovecii* and cytomegalovirus (CMV), should be considered in infants living with HIV, and when pneumonia is a presenting feature of HIV or a child is not receiving ART.[41,42]

Impact of HIV on radiological diagnosis

The interpretation of CXR changes is more difficult in HIV-infected children, as chronic radiological lung changes are common, especially with increasing age.[43] Increased bronchovascular markings, reticular densities, cavities, cysts and bronchiectasis are the most common chronic radiological changes.[44] Diffuse nodular densities and hilar or mediastinal adenopathy occurring in lymphocytic interstitial pneumonitis, may resemble TB.[44] Diffuse or scattered ground-glass opacification is a common manifestation of severe pneumocystis pneumonia (PCP) or CMV pneumonia, but no radiographic pattern is specific for either.[44] Bronchiolitis obliterans, characterised by fibrotic constriction or complete destruction of the bronchioles, should be considered in the differential diagnosis of multifocal consolidation and chronic hypoxia.[43] Perihilar airspace and reticular opacification, mainly in the lower lung zones, in addition to hilar lymphadenopathy and often large pleural effusion, are occasionally seen in CLWH with pulmonary manifestations of Kaposi sarcoma.[44]

Summary: HIV infection or exposure

Clinical signs of pneumonia are similar in HIV-infected and HIV-uninfected children; however, the former are more likely to present with severe disease, have higher rates of treatment failure and

death and pneumonia with opportunistic infections than immune-competent children (evidence level Ib).

Interpretation of CXR changes is more difficult in HIV-infected children, as chronic radiological lung changes are common, especially with longer survival (evidence level II).

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Conflicts of interest. None.

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