Guidelines for the Management of Community–Acquired Pneumonia in Children

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I. ETIOLOGY

A. The prevalent pathogen is different in different age groups.

B. Atypical pneumonia

1. Viral infections prevail in children younger than 5 years of age, especially respiratory syncytial virus. Other viral etiologies include influenza virus, parainfluenza virus, adenovirus, human metapneumovirus, rhinovirus, and cytomegalovirus.

2. Mycoplasma pneumoniae infections prevail in children older than 2-5 years of age. M. pneumoniae and Chlamydophila pneumoniae are responsible for 40-50% of atypical pneumonia in children of this age in Taiwan. Legionella pneumophila infection is relatively uncommon in children. Chlamydia trachomatis infection may occur in children younger than 6 months of age.

C. Pyogenic bacterial pneumonia

1. Streptococcus pneumoniae is the single most common cause of pyogenic bacterial pneumonia in children beyond the first few weeks of life. Haemophilus influenzae type b, Staphylococcus aureus are also possible offending bacteria pathogens in children younger than 5 years.

2. S. aureus is one common pathogen in pneumonia associated with chest trauma or influenza virus infection.

D. Mycobacterium tuberculosis infection is still prevalent in Taiwan and should be put into the list of differential diagnoses for community-acquired pneumonia (CAP) in children.

E. Mixed infection is not uncommon in children with CAP.

The causes of community-acquired pneumonia (CAP) in children as reported in the medical literature must be interpreted with caution, largely because many methods for assignment of etiology are inadequate. Pyogenic bacteria present the most difficult challenge, because the normal upper respiratory tract flora frequently contains potential pathogens and sputum collection may be difficult in young children. The presence of bacteremia confirms the cause, but blood culture is positive in less than one tenth of children with bacterial pneumonia.1

Epidemiologic information frequently is useful in guiding the search for the cause of pneumonia. Certain viruses, particularly respiratory syncytial virus (RSV), rhinoviruses, and influenza virus, as well as Mycoplasma pneumoniae, are strongly seasonal in temperate areas. However, as being located in subtropical region, the seasonal tendency of these pathogens in Taiwan is not as obvious as that in temperate areas. In other instances, the pattern of family illness can hint at the cause, especially the highly contagious influenza virus. Table 1 lists the etiological agents for pneumonia in children, and Table 2 shows the distribution of these agents in children by age.

Respiratory viruses are the most common cause of CAP in children younger than 5 years old. RSV is most prevalent in children younger than 1-2 years of age.4 Adenovirus has been reported to be associated with severe diseases in Taiwan.5 In temperate areas, RSV and influenza virus infections occur in winter epidemics, and parainfluenza viruses and rhinoviruses are more common in autumn and spring. Infections due to adenoviruses occur throughout the year. However, a recent study in Taiwan showed that monthly distribution of RSV infections in Northern Taiwan showed a bimodal pattern.
children with atypical pneumonia showed that 26% was infected by *M. pneumoniae*, 15% by *Chlamydophila pneumoniae*, and 6% by both of them. This study also suggested that mixed infection is not uncommon in children with CAP. A study on the etiology of atypical pneumonia in Asia, including Taiwan, showed that *M. pneumoniae* infected more children than adults, while the reverse was true for *C. pneumoniae* and *Legionella pneumophila*. Chlamydia trachomatis infection may occur in children younger than 6 months of age.

*Streptococcus pneumoniae* is the single most common cause of pyogenic bacterial pneumonia in children beyond the first few weeks of life. *Haemophilus influenzae* type b are also possible offending bacteria pathogens in children younger than 5 years. Nontypable *H. influenzae* is probably an uncommon cause of pneumonia, except in circumstances of underlying chronic lung disease, immunodeficiency, or aspiration. *Staphylococcus aureus* has also become an uncommon cause of pneumonia in the United States as well as in Taiwan over the past several years, but it must still be considered, especially in children younger than 2 years and in patients with severe, life-threatening pneumonia.

The recent emergence of community-acquired methicillin-resistant *S. aureus* that cause soft tissue and systemic infections in the community setting is an issue of concern and requires close surveillance. *S. aureus* is also a common pathogen in pneumonia associated with chest trauma or influenza virus infection.

### Table 1. Common Etiologic Agents of Community-Acquired Pneumonia in Children

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Mycoplasma</th>
<th>Chlamydia</th>
<th>Pyogenic bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory syncytial</td>
<td><em>Mycoplasma pneumoniae</em></td>
<td><em>Chlamydia trachomatis</em></td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>virus</td>
<td></td>
<td></td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Influenza A or B</td>
<td></td>
<td></td>
<td><em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td>Parainfluenza viruses 1,</td>
<td></td>
<td></td>
<td><em>Nontypable H. influenzae</em></td>
</tr>
<tr>
<td>2, and 3</td>
<td></td>
<td></td>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus</td>
<td></td>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Human metapneumovirus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Common Etiologies of Community-Acquired Pneumonia in Children by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacteria</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td>Group B <em>Streptococcus</em></td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other gram-negative enteric bacteria</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Listeria monocytogenes</em></td>
<td></td>
</tr>
<tr>
<td>2 months – 1 year</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em> type b</td>
<td>Influenza virus</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td>Parainfluenza virus</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Adenovirus</td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia trachomatis</em></td>
<td>Human metapneumovirus</td>
</tr>
<tr>
<td>2 – 5 years</td>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em> type b</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td></td>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Influenza virus</td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Parainfluenza virus</td>
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<td>Human metapneumovirus</td>
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<tr>
<td></td>
<td></td>
<td>Rhinovirus</td>
</tr>
<tr>
<td>6 – 18 years</td>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia pneumoniae</em></td>
<td>Influenza virus</td>
</tr>
<tr>
<td></td>
<td><em>Mycoplasma pneumoniae</em></td>
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streptococcal pneumonia are rapidly progressive and severe, frequently leading to hypoxemia and effusion within hours. *Mycobacterium tuberculosis* that is still prevalent in Taiwan should be put into the list of differential diagnoses for CAP in children.15

II. CLINICAL MANIFESTATIONS

A. Features of pyogenic bacteria pneumonia
1. Sudden deteriorated respiratory condition after an apparently mild respiratory infection.
2. Severely debilitated with poor activity when the body temperature is normal.
3. Tachypnea (respiratory rate > 60/min for infants < 11 months, > 40/min for children between 1 year and 4 years, and > 30/min for children older than 5 years).
4. Oxygen saturation ≤ 92%, cyanosis.
5. Septic signs, such as consciousness disturbance, bleeding tendency, and hypotension.
6. Signs of respiratory distress, including nasal flaring, grunting, and chest wall retraction.
7. Lung consolidation, cavity formation.

B. Features of atypical pneumonia:
2. Conjunctivitis, otitis media, skin rash, and wheezing may be more common.

There have been many studies conducted in an effort to differentiate bacterial etiologies of pneumonia from viral infections based on clinical manifestations. In general, none of the symptoms or signs can be considered specific. The onset of pyogenic bacterial pneumonia may be abrupt and may follow days of mild viral respiratory illness. The patient is ill, sometimes toxic appearing. Tachypnea, respiratory distress, hypoxemia, and lung consolidation or cavity formation are predictive of severe or pyogenic bacteria pneumonia16-18 A study from developing world showed that oxygen desaturation was associated with a greater risk of death, and tachypnea is closely related to hypoxemia.19 Several scoring systems have been proposed to predict the severity and mortality of CAP. However, none of them has been modified for children, and none has been examined in pediatric patients.19,20

In contrast to pyogenic bacterial pneumonia, children with atypical pneumonia, including those caused by *M. pneumoniae, C. pneumoniae, L. pneumophila* and viruses, usually appear healthy without apparent respiratory distress. Presence of arthralgia and erythema multiforme may suggest *M. pneumoniae* infection. As compared with pyogenic bacterial pneumonia, some studies suggest that children with atypical pneumonia may have a higher incidence of conjunctivitis,21 otitis media,22 and wheezing22,23 However, some features thought to be specific for viral illness were not observed more frequently in children with atypical pneumonia, including rhinorrhea, illness in family members, and myalgia.22,23

III. DIAGNOSIS

A. Acute phase reactants cannot reliably differentiate between pyogenic bacterial pneumonia and atypical pneumonia in children.

B. Image studies:
1. Chest radiography
   a. Chest radiography should be considered in children with an unexplained fever after excluding the possibility of common infectious diseases, and in those with a prolonged fever.
   b. Chest X-ray findings can hardly differentiate among different etiologies. Bulging interlobar fissures and cavitations are suggestive of pyogenic bacteria infection.
2. Chest ultrasonography is useful to evaluate the presence of consolidation and pleural effusion, and is helpful to guide thoracentesis or chest tubing.
3. Computerized tomography of the chest may provide details of pneumonia, and is indicated before surgical interventions.

C. Microbiological investigations:
1. Sputum:
   a. Gram stain, and acid-fast stain if necessary, should be done before the initiation of antibiotics.
   b. The result of sputum culture may not represent the true etiology of pneumonia. However, with a qualitative count of gram stain (polymorphonuclear cells > 25/high-power field and epithelium < 10/ high-power field, with or without phagocytosis of polymorphonuclear cells), it does provide some help to adjust the antimicrobial agent during the disease course.
   c. For patients with suspected *M. tuberculosis* infection, acid-fast stain and mycobacteria culture of the sputum should be done for at least 3 times. For children whose sputum is not available, gastric lavage for mycobacterial examination should be done in the early morning before meals for 3 consecutive days.
   d. Direct fluorescent antigen test is available for *L. pneumophila*.
2. Nasopharyngeal or oropharyngeal swab: The specimens may be sent for virus culture and viral antigen detection that are more useful for young
children.

3. Blood culture should be performed in all children with suspected pyogenic bacterial pneumonia.

4. A high titer of cold agglutinin may suggest mycoplasma pneumonia. However, its specificity is low.

5. A 4-fold rise of specific serum IgG titer or a single positive IgM response indicates acute infection.

6. Urinary antigen tests are available for *L. pneumophila* serogroup I and *S. pneumoniae*. Although the pneumococcal antigen test is less specific in children, it has a good negative predictive value for the diagnosis of *S. pneumoniae* pneumonia.

7. Tuberculin skin test should be performed when *M. tuberculosis* infection is suspected.

C. Invasive procedures:

1. The pleural fluid from thoracocentesis should be tested for:
   a. White count and differentials, protein, sugar, lactate dehydrogenase and pH value.
   b. Gram stain and acid-fast stain.
   c. Antigen test for *S. pneumoniae* and *H. influenzae* type b may be helpful.
   d. Culture for bacteria and, if suspected, virus and *M. tuberculosis*.

2. Bronchoalveolar lavage and lung biopsy may be considered in some difficult cases.

White cell count, neutrophil count, percentage of immature neutrophil, erythrocyte sedimentation rate, and C-reactive protein (CRP) may reflect the severity of infections, and are therefore believed to be able to differentiate between pyogenic and nonpyogenic infections. However, serum CRP was not useful to distinguish between pneumococcal, chlamydial, or viral etiology in children with pneumonia in a prospective study. Following an acute-phase stimulus, CRP values peak at approximately 48 hours. Timing of CRP test should be considered in interpretation. Acute phase reactants may only be useful to monitor the treatment response, and to distinguish between fever and hyperthermia that is not caused by an inflammatory response.

There has been some debates about the optimal timing for chest X-ray examination in children with respiratory symptoms. One study of 522 children aged 2 to 59 months that were randomly allocated to have a chest radiograph or not showed that there was a marginal improvement in time to recovery which was not clinically significant. It was concluded that routine use of chest radiography is not beneficial in ambulatory children aged over 2 months with acute lower respiratory-tract infection. Another study of 278 children aged 5 years or less suggested that chest radiography should be considered a routine diagnostic test in children with a temperature of 39 °C or greater and white count of 20,000/mm³ or greater without an alternative major source of infection. In that study, pneumonia was found in 32 of 79 (40%) of those with findings suggestive of pneumonia and in 38 of 146 (26%) of those without clinical evidence of pneumonia. Although chest radiography should not be performed routinely in children with mild uncomplicated acute lower respiratory tract infection, it may be indicated in selective patients, including an unexplained fever after excluding the possibility of common infectious diseases, and a prolonged fever with or without respiratory manifestations.

Chest X-ray findings can hardly differentiate among different etiologies, especially for interstitial infiltrations and pneumonic patches. Lung consolidation and pleural effusion may be observed in pyogenic bacterial pneumonia and pneumonia caused by *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. Bulging interlobar fissures and cavitations are suggestive of pyogenic bacteria infection. Chest ultrasonography is simple, ready to use, and not associated with radiation. It is useful to evaluate the presence of consolidation and pleural effusion, and is helpful to guide thoracocentesis or chest tubing, and for follow-up. Therefore, it may be considered when chest X-ray shows the presence of consolidation or pleural effusion.

Computerized tomography (CT) of the chest may provide details of pneumonia, including the extent of consolidation, cavitation, lung abscess, and empyema. It is indicated before surgical interventions, such as video-assisted thoracoscopic surgery (VATS), and decortication of empyema. It may also be useful to evaluate complicated pneumonia with poor clinical response. High-resolution CT has been suggested to be more sensitive than chest radiograph to detect pulmonary infiltrates. However, it should not be used routinely.

For the majority of patients treated as outpatients, a specific microbiological diagnosis may not be necessary. The investigations are important for patients admitted to hospital with pneumonia. Sputum gram staining, and acid-fast staining if necessary, should be performed before the initiation of antibiotics. The sputum may be hard to be obtained in children and the result of sputum culture may not represent the true etiology of pneumonia. However, with a quantitative count of gram stain, it does provide some help to adjust the antimicrobial agent later on.

In Taiwan, it is recommended that at least 3 sputum specimens should be sent for acid-fast stain and mycobacterial culture in patients with suspected *M. tuberculosis* infection. Because the sputum cannot be obtained in many children, gastric lavage in the early morning before meals for 3 consecutive days is also
a proper specimen for mycobacteria study.  

Direct fluorescent antigen test is a reliable test for *L. pneumophila*. It may be performed in selected patients. Sputum obtained from bronchoscope has better sensitivity. 

Because viral etiologies are more prevalent in younger children with CAP, nasopharyngeal or oropharyngeal swab may be sent for virus culture and viral antigen detection, including RSV, influenza virus A and B, parainfluenza virus, and adenovirus. However, laboratory quality should be certified for these tests. 

Blood culture should be performed in all children with suspected bacterial pneumonia before receiving antibiotics. However, the isolation rate is no more than 10-20%.  

Cold agglutinin is a nonspecific antibody response in *M. pneumonaeae* infection. It is a sensitive test, but its specificity is low and an elevated titer may also be seen in other causes of CAP. Several serological tests are available for the diagnosis of *M. pneumonaeae, Chlamydophila pneumonaeae, Chlamydia trachomatis, L. pneumophila*, and common respiratory viruses. A 4-fold rise of IgG titer or a single positive IgM response indicates acute infection. A single high titer of IgG is not diagnostic. 

Legionella urinary antigen test identifies only *L. pneumophila* serogroup I, which is claimed to be the most common type causing clinical illness. A study in Taiwan showed that urine antigen test can detect only 17.3% of 237 patients with *L. pneumophila* infection.  

A negative test does no exclude the diagnosis. 

Pneumococcal urinary antigen test is an acceptable test to augment diagnostic methods for *S. pneumonaeae* infection. The sensitivity ranged between 50% and 80%, and the specificity is about 90% in adults. Several studies involving children have documented the lack of specificity. Although many authors suggest that a low specificity of the test may be attributed to that the test may give a false-positive result in children with colonization, it is more appropriate to say that the test may also be positive in *S. pneumonaeae* infections other than pneumonia, such as otitis media. The test has a high sensitivity and a good negative predictive value for the diagnosis of *S. pneumonaeae* pneumonia in children. 

Bacille Calmette-Guérin (BCG) is routinely given to children in Taiwan. Although the vaccination may interfere with the interpretation of tuberculin reaction, studies in Taiwan showed that BCG vaccination did not appear to limit the usefulness of tuberculin skin test as a tool for diagnosing tuberculosis. The tuberculin reactivity toward BCG is usually lost 5-10 yr after vaccination. 

Significant pleural effusion should be aspirated for etiological diagnosis, especially when the effusion is > 10 mm in thickness on the lateral decubitus view or chest ultrasonography. Gram stain and acid-fast stain should be routinely done. White count and differentials, protein, sugar, lactate dehydrogenase and pH value are helpful to differentiate among transudate, and uncomplicated or complicated parapneumonic pleural effusions. The sensitivity of culture to define the offending bacteria is usually limited but can be improved by antigen detection. 

Culture for *M. tuberculoses* and viruses, though being less frequently seen, should be done in suspected cases. 

Invasive procedures, including bronchoalveolar lavage and lung biopsy, should not be routinely done. Analysis of sputum from bronchoalveolar lavage may have a better correlation with pneumonia. However, it is technically difficult in young children and can only be considered in some difficult cases. 

**IV. GENERAL MANAGEMENT**

**A. Decision for hospitalization**

1. Children with the following conditions that may be suggestive of a grave illness are not recommended to be cared at home: 
   a. Features of severe bacterial pneumonia (see II-A). 
   b. Signs of dehydration. 
   c. Neonates and children with immunodeficiency. 
   d. Caretakers not able to provide appropriate observation or supervision. 

2. If the clinical condition is aggravated, or is not improving after 48 hours on treatment at home, the child should be reviewed by a pediatric specialist. 

**B. Children who have hypoxemia or respiratory distress should receive oxygen therapy.** 

**C. Intravenous fluids, if necessary, may be given at 80% maintenance level with monitoring of serum electrolytes.** 

Children with CAP may be cared at home, especially for those caused by atypical pathogens. As listed in II-A, several clinical manifestations are predictive for a severe bacteria pneumonia that should be cared in hospitals. Oral intake usually decreases in children with pneumonia. If there are obvious signs of dehydration, the child should also be hospitalized. CAP in neonates and children with immunodeficiency are prone to being more severe. Therefore, they should be treated more aggressively in the hospital. 

Hypoxemia and respiratory distress are important risk factors of a severe disease. Oxygen therapy given by nasal cannula, head box, face mask, or oxygen tent
should be given to children with hypoxemia, especially for those with oxygen saturation ≤ 92%. If blood oxygenation is not improved after oxygen therapy, patient should be cared for at an intensive care unit with positive-pressure respiratory support, such as intubation and use of ventilator.

V. ANTIBIOTIC THERAPY

A. Principle
1. Empiric use of antibiotics should take into consideration the age and the disease severity of the patients. Appropriate antibiotics should be given as soon as possible after registration for hospitalized patients.
2. Parenteral antibiotics should be given to children with severe pneumonia.
3. If fever or some grave clinical manifestations persist beyond 48 hours after treatment, the treatment plan should be re-evaluated and a follow-up chest image study should be considered.
4. Oral switch of antibiotics: If the clinical condition improves rapidly with all of the following characteristics suggestive of a stabilized illness, intravenous antibiotics may be considered to be switched to oral ones. 
   a. Absence of septic signs, empyema, necrotizing pneumonia and lung abscess.
   b. Stabilized vital signs for at least 48 hours, including body temperature, heart rate, respiratory rate, and blood pressure.
   c. No growth on blood culture.
   d. May be fed orally.
5. Duration of antibiotic treatment
   a. Mycoplasma pneumonia and chlamydia pneumonia may be treated by appropriate oral antibiotics for 10 days. If azithromycin is used, the treatment should be continued for only 3-5 days.
   b. Legionnaires' disease: For immunocompetent children, azithromycin may be used for 5-10 days, and other macrolides and fluoroquinolones may be used for 10-14 days. For immunocompromised children, macrolides plus fluoroquinolones or rifampin may be used for 14-21 days.
   c. Antibiotics should be given according to the treatment response, and are usually used for at least 7-10 days.
   d. Duration of antibiotic therapy may need to be prolonged in complicated infections, such as those complicated by bacteremia or meningitis, Pseudomonas aeruginosa infection, empyema, necrotizing pneumonia, and lung abscess.

B. Choice of antibiotics when the pathogen is known:
Current antibiotic-resistance rate of some important respiratory pathogens in Taiwan include 70% of penicillin-nonsusceptible S. pneumoniae (minimum inhibitory concentration ≥ 0.12 μg/mL), about 60% of β-lactamase-producing H. influenzae, and 50-70% of community-acquired methicillin-resistant S. aureus.

<table>
<thead>
<tr>
<th>Antibiotic of choice</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae Penicillin MIC</td>
<td></td>
</tr>
</tbody>
</table>
< 1 μg/mL | Penicillin, ampicillin or amoxicillin  
≥ 1 and < 4 μg/mL | Penicillin, ampicillin or amoxicillin  
≥ 4 μg/mL | 3rd or 4th cephalosporins, vancomycin or teicoplanin  
1st cephalosporinb  
3rd or 4th cephalosporinsa  
Vancomycin or teicoplanin ± rifampicin  
Linezolid |
| Haemophilus influenzae β-lactamase(-) | Ampicillin or amoxicillin  
β-lactamase(+) | Amoxicillin/clavulanate, ampicillin/sulbactam or 2nd cephalosporinsb  
New macrolidesc or TMP/SMXd  
3rd cephalosporins or new macrolides |
| Moraxella catarrhalis | Amoxicillin/clavulanate, ampicillin/sulbactam or 2nd cephalosporins  
Erythromycin, new macrolides or 3rd cephalosporins |
| Staphylococcus aureus Oxacillin-sensitive | Oxacillin, 1st cephalosporin  
Oxacillin-resistant | Vancomycin or teicoplanin  
Vancomycin or teicoplanin  
Linezolid |
| Mycoplasma pneumoniae | Erythromycin or new macrolides  
tetracyclinesf for those older than 8 years |
| Chlamydia pneumoniae | Erythromycin or new macrolides  
tetracyclines for those older than 8 years |
| Chlamydia trachomatis | Erythromycin or new macrolides |
Legionella species | New macrolides | Erythromycin or new macrolides + rifampicin, fluoroquinolones\(^8\)
---|---|---
\(^3\) cephalosporins: cefotaxime, ceftriaxone; \(^4\) cephalosporins: cefepime.
\(^1\) cephalosporin: cefazolin.
\(^5\) New macrolides: azithromycin, clarithromycin.
\(^6\) TMP/SMX: trimethoprim/sulfamethoxazole.
\(^2\) cephalosporins: cefuroxime.
\(^7\) Tetracyclines: tetracycline, minocycline, doxycycline.
\(^8\) Fluoroquinolones: ciprofloxacin.

B. Choice of antibiotics when the pathogen is unknown:

<table>
<thead>
<tr>
<th>Antibiotic of choice</th>
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</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td>Ampicillin + aminoglycosides</td>
</tr>
<tr>
<td>2 months - 1 year</td>
<td>Penicillin or Ampicillin or Amoxicillin/clavulanate or Ampicillin/subactam</td>
</tr>
<tr>
<td>2 - 5 years</td>
<td>Penicillin or Ampicillin or Amoxicillin/clavulanate or Ampicillin/subactam (\pm) Macrolides</td>
</tr>
<tr>
<td>6 - 18 years</td>
<td>Penicillin (\pm) Macrolides</td>
</tr>
</tbody>
</table>

D. Choice of antibiotics under special circumstances:
1. Broad-spectrum and potent antibiotics should be used in children with sepsis, meningitis, or complications that may endanger the life.
2. For children with disorders such as bronchiectasis, chronic lung disease, and severe neuromuscular disorders and have a history of recurrent pneumonia, repetitive use of antibiotics, or prolonged use of steroids, enteric gram-negative bacteria, including P. aeruginosa, are more likely to be the offending pathogen. Empiric therapy may include antipseudomonal \(\beta\) -lactams with or without aminoglycosides.
3. When S. aureus infection is a concern, such as chest trauma or influenza-associated pneumonia, antibiotics effective against methicillin-resistant S. aureus may be added to the empiric therapy.

E. Recommended dosage of empirical antibiotics (for children older than 1 month of age):
1. Penicillin: 300,000-400,000 units/kg/day, q6-8h.
2. Ampicillin: 150-200 mg/kg/day, q6h.
3. Amoxicillin: 80-90 mg/kg/day, po tid.
4. Oxacillin: 100-300 mg/kg/day, q4-6h.
5. Ampicillin/subactam: 150-200 ampicillin mg/kg/day, q6-8h.
6. Amoxicillin/clavulanate: 150-200 amoxicillin mg/kg/day, iv q6-8h; 80-90 amoxicillin mg/kg/day, po bid-tid.
7. Cefazolin: 50-100 mg/kg/day, iv q8-6h.
8. Cefuroxime: 100-200 mg/kg/day, iv q6-8h; 20-30 mg/kg/day, po bid, may double the dose for severe infection.
9. Ticarcillin/clavulanate: 200-300 ticarcillin mg/kg/day, q6-8h.
10. Piperacillin/tazobactam: 200-300 piperacillin mg/kg/day, q6-8h.
11. Cefotaxime: 150-200 mg/kg/day, q6h.
12. Ceftriaxone: 100 mg/kg/day, q12h - qd.
13. Cefazidime: 100-150 mg/kg/day, q6-8h.
14. Ceftizoxime: 100-150 mg/kg/day, q8-12h.
15. Imipenem: 60-100 mg/kg/day, q6h.
16. Meropenem: 60-100 mg/kg/day, q6-8h.
17. Erythromycin: 40 mg/kg/day, q6h.
18. Clarithromycin: 15 mg/kg/day, q12h.
19. Azithromycin: 10-12 mg/kg/day, qd.
20. Tetracyclines: 25-50 mg/kg/day, po bid-qid.
Age and disease severity are the two most important factors in deciding whether antibiotics should be used or which antibiotics should be chosen. For example, viral infections are more prevalent in young children, and it is recommended that young children presenting with mild symptoms of lower respiratory tract infection need not be treated with antibiotics. Studies showed that initiation of antibiotics within 4 to 8 hours after arrival at hospital correlated strongly with the outcome. Appropriate antibiotics should be given as soon as possible after registration for hospitalized patients.

Orally administered antibiotics are safe and effective for children with community-acquired pneumonia that is not associated with clinical manifestations suggestive of a grave illness. Parenteral antibiotics can ensure a rapidly rising high serum concentration and should be given to children with clinical manifestations suggestive of a severe pneumonia and to those who cannot be fed orally.

Some viral pneumonia may have a prolonged fever, and some bacterial pneumonia may have a persistent fever after using appropriate antibiotics, especially for those with consolidation and pleural effusion. However, clinical conditions of bacteria pneumonia that are responsive to antibiotics usually improved within 48 hours after treatment with defervescence. If fever or some grave clinical manifestations persist beyond 48 hours after treatment, the treatment plan should be re-evaluated and a follow-up chest image study should be considered.

There have been limited data published regarding intravenous-to-oral sequential antibiotic therapy in Taiwan. Some randomized studies suggested that intravenous-to-oral switch of antibiotics may be feasible for some clinically stable and antibiotic-responsive CAP. Such a practice may be able to reduce the cost of treatment and the length of stay in the hospital. We recommend that oral switch of antibiotics may be applied to CAP in children without evidence of sepsis, empyema, necrotizing pneumonia, and lung abscess when the vital signs have been stabilized for at least 48 hours and when the patient can be fed orally. Generally, the antibiotic switch can take place after 2-4 days of intravenous therapy.

There is no appropriate randomized study to define the optimal duration of antibiotic therapy for CAP. Most recommendations are conjectural, and many physicians recommend treatment for 1-2 weeks. The recommended durations of treatment in this guideline are based on the experiences of experts and some statements in textbooks. Seven to 10 days of treatment is usually enough with 2 exceptions. One is Legionnaires' disease that may be more severe than other causes of atypical pneumonia, especially when it occurs in immunocompromised children. The recommended duration is longer. The other is complicated pneumonia that may require a longer duration of treatment, including those complicated by bacteremia or meningitis, Pseudomonas aeruginosa infection, empyema, necrotizing pneumonia, and lung abscess. Community-acquired P. aeruginosa sepsis with or without pneumonia is most frequently seen in infants.

When the pathogen is known, the antibiotic should be chosen according to the antibiotic susceptibility pattern. Antibiotic resistance among pneumococci is increasing and the incidence of severe pneumococcal pneumonia is apparently increasing in recent years. Being the same as our previous version of guideline, a penicillin minimum inhibitory concentration (MIC) of < 1 µg/mL was defined as penicillin susceptible, MIC ≥ 4 µg/mL as penicillin resistant, and an intermediate MIC as penicillin intermediate. Recently, penicillin MIC's of about 70% of S. pneumoniae strains in Taiwan are ≥0.12 µg/mL, while only less than 5% is penicillin-resistant (MIC ≥ 4 µg/mL). Therefore, most penicillin-nonsusceptible S. pneumoniae infection can be treated by a high dose of penicillin and its analogue. On the other hand, erythromycin resistance in S. pneumoniae has remained high (94%) in Taiwan in recent years. Likewise, trimethoprim-sulfamethoxazole resistance rate is also high (65%).

Recent studies in Taiwan showed that 56% of H. influenzae isolates produce β-lactamase, as did nearly all Moraxella catarrhalis isolates (95.7%). Only 1.7% of H. influenzae were β-lactamase negative and amoxicillin resistant. Antibiotics used for these gram-negative bacteria should be stable to β-lactamase. The resistance rate to trimethoprim-sulfamethoxazole is 52% for H. influenzae.

Having being a predominant pathogen in nosocomial infections in Taiwan for many years, methicillin-resistant S. aureus is now becoming more and more common.
in community-acquired infections. Recent data demonstrated that 50-70% of community strains of S. aureus obtained from pediatric patients is resistant to methicillin.\textsuperscript{12,13} Vancomycin and other agents active against methicillin-resistance S. aureus may be considered in selected cases, especially for those with chest trauma and influenza.\textsuperscript{44}

*M. pneumoniae, C. pneumoniae* and *C. trachomatis* are rarely resistant to erythromycin and other macrolides that should be the drug of choice for these infections. Different macrolides have similar therapeutic efficacy.\textsuperscript{6} Tetracyclines may be used as an alternative only when the child is older than 8 years to avoid their potential detrimental effects on bone and teeth. Although fluoroquinolones may be used as the first-line drug for treating *L. pneumophila* infection,\textsuperscript{32,55} new macrolides are a more preferred agent in children. Rifampin or fluoroquinolones may be added in severe infections.

When the pathogen is unknown, either before the culture result is available or due to a negative result of microbiological test, antibiotics may be given empirically based on the knowledge of predominant pathogens in each age groups.

For neonates younger than 1 month, *Escherichia coli*, group B streptococcus and other bacteria are common pathogens. They may be treated empirically by ampicillin + aminoglycosides, or by ampicillin + cefotaxime or ceftriaxone when meningitis is a concern. Common bacterial pathogens of CAP in children between 2 months and 5 years of age include *S. pneumoniae* and *H. influenzae* type b. \beta-lactams stable to \beta-lactamase may be used empirically. *S. pneumoniae* becomes the single most important etiology of CAP in children beyond 6 years of age. Penicillin may be used as empirical therapy for clinically stable patients.

*M. pneumoniae* and *C. pneumoniae* infections are not infrequent after 2 years of age.\textsuperscript{6,7} For children older than 2 years with suspected atypical pneumonia, macrolides are the antibiotic of choice. However, such infections are not totally absent in children younger than 2 years,\textsuperscript{6} and *C. trachomatis* is a possible etiology of CAP in infants.\textsuperscript{8} Macrolide antibiotics may be used in special circumstances.

The choice of antibiotics should also take into account the severity of illness and comorbidities. Several guidelines for management of CAP in adults stratify patients into groups based on site of therapy (i.e. outpatient, inpatient, or intensive care unit), comorbidities (including cardiopulmonary disease, diabetes mellitus, renal failure, malignancy), and risk factors for infection with drug-resistant bacteria.\textsuperscript{12,55,56} To avoid too many stratifications, the working group choose to stratify pediatric patients by the age only. However, some points deserve further attention.

A few retrospective studies suggested that dual therapy with \beta-lactams and a macrolide may reduce mortality associated with bacteremic pneumococcal pneumonia.\textsuperscript{57,58} Two possible explanations are the immunonodulating effect of macrolides and a concomitant infection by atypical pathogens that may be susceptible to macrolides. A well-designed prospective study is needed to prove such an observation, and the data in pediatric patients are still lacking. However, adding a macrolide for children with suspected pyogenic pneumonia may be warranted since mixed infections are not uncommon in children with CAP.

With life-threatening complications, such as sepsis and meningitis, CAP in children may be treated empirically with broad-spectrum and potent antibiotics, such as vancomycin plus a third-generation cephalosporin or other antibiotics effective against commonly seen gram-negative bacteria.

Enteric gram-negative bacteria, such as *P. aeruginosa*, may pose some impact on selection of an appropriate antibiotic for treatment of CAP. Several risk factors have been recognized in adult patients.\textsuperscript{86} Patients who reside in a nursing home, or have underlying cardiopulmonary disease or multiple comorbidities, or have received recent antimicrobial therapy are more likely to be infected by enteric organisms. Risk factors for *P. aeruginosa* infection include structural lung disease (e.g. bronchiectasis), steroid therapy, recent use of broad-spectrum antibiotic, and malnutrition. Although similar data are lacking for children, the working group makes similar recommendations. When children with disorders such as bronchiectasis, chronic lung disease, and severe neuromuscular disorders have a history of recurrent pneumonia, repetitive use of antibiotics, or prolonged use of steroids, they tended to be infected by gram-negative bacteria, including *P. aeruginosa*. Empiric therapy may include antipseudomonal \beta-lactams (including ceftazidime, piperacillin, ticarcillin/clavulanate, piperacillin/tazobactam, ceftazidime, imipenem, and meropenem) with or without aminoglycosides.

Because some antibiotic-resistant bacteria, especially penicillin-nonsusceptible *S. pneumoniae*, are highly prevalent in Taiwan, the dosage of some antibiotics should be modified. As mentioned before, less than 5% of penicillin-nonsusceptible *S. pneumoniae* is truly resistant to penicillin with a MIC ≥ 4 \mu g/mL in Taiwan,\textsuperscript{85} increasing the dose of penicillin, ampicillin, amoxicillin, ampicillin/sulbactam, amoxicillin/clavulanate, cefuroxime, and cefotaxime may be an effective way to treat infections caused by penicillin-intermediate *S. pneumoniae*. The recommended dosage of various antibiotics in present guideline is for empirical use of antibiotics. The dosage of antibiotics may be adjusted when the pathogen and its antibiotic susceptibility pattern are known. For
example, when dealing with penicillin-susceptible *S. pneumoniae* infection, the dose of penicillin may be lowered down.

As suggested by recent pharmacokinetic and pharmacodynamic studies, some antibiotics are time-dependent for their therapeutic effect, including β-lactams and macrolides. Frequent dosing may improve their performance. On the other hand, some antibiotics are concentration-dependent, including aminoglycosides and fluoroquinolones. Such antibiotics should be given with a longer dosing interval to maximize their therapeutic effect. In the era of increasing resistance, an dosing schedule with optimized pharmacokinetic and pharmacodynamic features can not only bring about a better treatment response, but also prevent the emergence of resistant bacteria. The recommended dosage in this guideline was set up according to this principle.

### VI. POST-TREATMENT EVALUATION AND MANAGEMENT OF COMPLICATION

A. If the fever persists, the clinical condition is not improved, or aggravating signs appeared after treatment, the following conditions should be considered.

1. Inadequate dose of antibiotics.
2. Antimicrobials not effective for offending pathogen, such as antibiotic-resistant bacteria, tuberculosis.
3. Viral infection or mixed infection.
4. Extrapulmonary focus of infection.
5. Complication of pneumonia, such as lung abscess, empyema.
6. Drug fever.

B. Complication of pneumonia:

1. Pleural effusion, empyema.
2. Necrotizing pneumonia, lung abscess.
3. Acute respiratory distress syndrome.
4. Others, such as bronchopleural fistula.

C. Management of pleural effusion and empyema:

1. Diagnosis: lateral decubitus chest radiography or chest ultrasonography. The latter is preferred.
2. Pleural tapping: Examinations of pleural fluid should include white count and differentials, pH value, glucose, protein, gram stain, acid-fast stain, bacterial culture, mycobacteria culture. Bacteria antigen detection may also be considered.
3. With one of the following conditions, drainage of pleural fluid should be required:
   a. Pus-like effusion.
   b. Positive finding of gram stain or bacterial culture of pleural fluid.
   c. Large amount of fibrinous substances or septations in pleural cavity.
   d. Massive pleural effusion associated with respiratory distress.
   e. pH of pleural fluid < 7.2.
4. Draining procedure
   a. Simple chest tube drainage: not recommended.
   b. Chest tube drainage with fibrinolytic agents: Use streptokinase 2,500 U/mL or urokinase 1,000 U/mL with a dose of 3-4 mL/kg that does not exceed 100 mL. The agent may be given once per day with retention of the agent for 2-4 hours each time. The therapy may be instituted for 2-3 days or until there is a significant improvement of chest images. Tissue plasminogen activator may be used with a dose of 2-5 gm in 50-250 mL saline.
   c. Video-assisted thoracoscopic surgery (VATS): Computerized tomography of the chest should be performed previous to this procedure to delineate the extent of pleural effusion. Early VATS that is performed within 4 days after the diagnosis is more effective than late VATS.
   d. If the above mentioned draining procedures fail to improve the condition, such as persistent high fever and severe respiratory distress, open surgery for drainage may be considered.

D. Management of necrotizing pneumonia and lung abscess:

- Chest ultrasonography or computerized tomography should be performed. If the clinical condition does not improve after appropriate antimicrobial therapy and drainage, open surgery may be considered.

If the fever persists, the clinical condition is not improved or even aggravated after treatment, several possibilities should be considered. Because penicillin-nonsusceptible *S. pneumoniae* is highly prevalent in Taiwan, an adequate dose of antibiotics as mentioned in present guideline is a prerequisite to ensure treatment success. For young infants and children with risk factors, antibiotics with a broader antibacterial spectrum may be necessary to be effective against potential pathogens, including methicillin-resistant *S. aureus* and enteric gram-negative bacteria. As mentioned previously, *M. tuberculosis* infection is prevalent in Taiwan and should be regarded as a possible etiology in CAP unresponsive to empiric antibiotic therapy.

Viral infection and extrapulmonary focus of infection are also possible causes for an unresponsive CAP. A study in Taiwan showed that children with a severe pneumonic change (consolidation or pleural effusion) or extrapulmonary manifestations (e.g. encephalitis, hepatitis) tended to have a prolonged fever after appropriate macrolide treatment in children with either *M. pneumoniae* or *C. pneumoniae* infection. Adequate drainage of lung abscess and empyema may be necessary
for some complicated pneumonia.

Drug fever is easily overlooked because affected patients may have an extremely high temperature and a high CRP value. Sulfonamides and β-lactams are common causes of drug fever. However, it should be assumed that any drug can cause drug fever, including nonantibiotics.60 Fever may develop a few days after using an antibiotic.61 A relatively good activity with re-emergence of fever after defervescence for some days after treatment is characteristic for drug fever. Other helpful clues to drug fever are skin rashes, relative bradycardia, neutropenia, eosinophilia, atypical lymphocytosis, elevations of the serum transaminases.61,62 The diagnosis of drug fever may be confirmed by observing a subsidence of fever after withholding the offending medication. Drug fever usually subsides within 72 hours after the sensitizing drug is discontinued if a rash is not present.61

Parapneumonic pleural effusion is not uncommon in children with bacterial pneumonia and is a common cause of prolonged fever after treatment. A study in Taiwan showed that 56% of pneumococcus pneumonia in children is complicated.50 It has been recommended that for all adult patients with acute bacterial pneumonia, the presence of a parapneumonic effusion should be considered.63 The effusion may be delineated by lateral decubitus chest radiography or by chest ultrasonography. Chest ultrasonography is preferred because it is more accurate relative to lateral decubitus chest radiography for the diagnosis of small pleural effusions.64

Aspirated pleural fluid should be sent for necessary tests. Some studies showed that commercially available pneumococcal antigen test that was designed for cerebrospinal fluid samples may also be useful for pleural fluid.65,66 Although available data are limited, the working group suggests that such a bacteria antigen test may be used for pleural fluid when S. pneumoniae infection is one of the possible pathogens.

It is a common agreement that a frankly purulent effusion or an effusion containing bacteria as evidenced by either culture or gram stain should be drained to hasten the recovery and to avoid complications. Dilemma occurs when the effusion does not appear purulent. A meta-analysis suggested that a low pH < 7.21–7.29 was the most accurate predictor of the need for drainage.67 The cut-off point for pH is controversial. The present recommendation adopts a pH of 7.2 as a cut-off, similar to that recommended by the American College of Chest Physicians.68

There are several drainage procedures. A recent review showed that the pooled mortality was higher for the no drainage (6.6%), therapeutic thoracentesis (10.3%), and tube thoracostomy (8.8%) than for the fibrinolytic (4.3%), VATS (4.8%), and surgery (1.9%). The pooled proportion of patients needing a second intervention was also higher for the no drainage, therapeutic thoracentesis, and tube thoracostomy management approaches.69

Adding streptokinase, urokinase or tissue plasminogen activator into the chest cavity may facilitate the drainage by causing lysis of fibrins and septations. Fibrinolytic agents are resolved in normal saline that is instituted into a properly positioned chest tube. The drainage is held for several hours for fibrinolytic agents to take effect. Several studies in Taiwan have shown that intrapleural fibrinolytic treatment is safe and effective in children, and it can obviate the need for surgery.68,69 There is not a consensus on the dosage of fibrinolytic agents. However, the working group suggests one dosage schedule according to the experience in Taiwan.

Most studies agree that debridement of the pleural space by VATS is effective for the management of pleural empyema, including studies in children. Data also suggested that the main prognostic factor for thoracoscopic treatment of pleural empyema is the interval between diagnosis and surgery.70,71 A 4-day limit, corresponding to the natural process of empyema organization, may significantly affect the efficacy of VATS.70,71 Therefore, VATS should be attempted within 4 days after diagnosis when necessary. Open surgery is another option for the treatment of pleural empyema in children.

Necrotizing pneumonia and lung abscess are not uncommon in children with CAP. Diagnosis may be confirmed by ultrasonography or computerized tomography. Prolonged antibiotic therapy may be required. Infrequently, open surgery may be needed in complicated cases refractory to medical therapy.

VII. PREVENTION

A. General principles: reduce the risk of exposure to respiratory pathogens by droplet precautions.

B. Immunization:

1. Bacille Calmette-Guérin vaccine: routine for all neonates and 7-year-old children who has a negative tuberculin reaction.

2. Influenza vaccine:
   a. Routine for children aged 6–23 months.
   b. Recommended for children older than 23 months with high-risk conditions.

3. Pneumococcal vaccine: 23-valent pneumococcal polysaccharide vaccine (PPV23) for children older than 2 years and 7-valent pneumococcal conjugate vaccine (PCV7) for children older than 2 months. Recommended schedule for those having not received pneumococcal vaccines:
C. Preventive therapy:

1. **Tuberculosis:** isoniazid 10 mg/kg/day (maximum 300 mg/day) for 9 months recommended for children ≤12 years with evidence of latent tuberculosis infection and a history of close contact with patients with infectious tuberculosis.

2. **Haemophilus influenzae** type b infection: rifampin 20 mg/kg (maximum 600 mg) daily for 4 days for all household contacts when at least 1 contact is younger than 4 years of age.

Pathogens responsible for CAP are transmitted by droplet, while most bacterial pneumonia may be complications of some preceding virus infection. Preventive measures for CAP include droplet precautions for hospitalized children, strict hand hygiene procedures, and that infected children should be excluded from school and day care facilities until they are no longer considered contagious.

According to the guidelines for the diagnosis and treatment of tuberculosis in Taiwan, one dose of BCG should be given to all neonates with a body weight ≥2,500 gm. Tuberculin skin test is done at school entry (7 years of age) for children whose BCG scar is ≤2 mm in diameter. One dose of BCG should be given to those who have a negative tuberculin reaction.

Currently, influenza vaccine is a routine for children aged between 6 and 23 months in Taiwan. The vaccine is also recommended for children older than 23 months of age with risk factors, including chronic pulmonary diseases (e.g. bronchopulmonary dysplasia, cystic fibrosis, bronchiolitis obliterans, laryngotracheomalasia, asthma), hemodynamically significant cardiac disease, immunosuppressive disorders or therapy, human immunodeficiency virus infection, hemoglobinopathies, disorders requiring long term salicylate therapy (e.g. rheumatoid arthritis, Kawasaki disease), chronic renal dysfunction, chronic metabolic disease (including diabetes mellitus), and any condition that can compromise respiratory function or handling of respiratory tract secretions or that can increase the risk of aspiration.

Two pneumococcal vaccines are available in Taiwan, including a 23-valent polysaccharide pneumococcal vaccine (PPV23) for use in children aged over 2 year, and a 7-valent pneumococcal conjugate vaccine (PCV7) for children between 2 months and 9 years of age. The PCV7 is recommended for routine vaccination at 2, 4, 6, and 12-18 months of age. Catch-up vaccination is also recommended for children up to 23 months of age with fewer doses of PCV7. The cost-effectiveness of pneumococcal vaccines in healthy children between 24 and 59 months of age remain to be studied. Pneumococcal vaccines may be given to all children older than 24 months of age with risk factors, including hemoglobinopathies, congenital or acquired immune deficiency, human immunodeficiency virus infection, chronic pulmonary disease, chronic renal disorders, diabetes mellitus, anatomical abnormalities associated with higher rates or severity, cerebrospinal leaks, hemodynamically significant heart disease, and chronic pulmonary disease.

Recent revision of the guidelines for the diagnosis and treatment of tuberculosis in Taiwan recommends that isoniazid chemoprophylaxis may be given to children ≤12 years with evidence of latent tuberculosis infection by the tuberculin reaction and a history of close contact with patients with infectious tuberculosis. The risk of invasive **Haemophilus influenzae** type b disease is increased among household contacts who are less than 4 years of age. Rifampin 20 mg/kg (maximum 600 mg) daily for 4 days is recommended for all household contacts in such occasions regardless of the age of household contacts and the **Haemophilus influenzae** type b vaccination history.

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