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Japanese Guidelines for the Management of Respiratory Infectious Diseases in Children 2007 with focus on pneumonia

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Abstract Members of the Japanese Society of Pediatric Pulmonology and the Japanese Society for Pediatric Infectious Diseases developed the Guidelines for the Management of Respiratory Infectious Diseases in Children with the objective of facilitating the appropriate diagnosis and treatment of childhood respiratory infections. To date, a first edition (2004) and a revised edition (2007) have been issued. Many problems complicate the diagnosis of the pathogens responsible for bronchopulmonary infections in children. The Guidelines were the first pediatric guidelines in the world to recommend treatment with antimicrobials suited to causative pathogens as identified from cultures of sputum and other clinical specimens collected from infection sites and satisfying assessment criteria. The major causative microorganisms for pneumonia in infants and children were revealed to be Streptococcus pneumoniae, Haemophilus influenzae and Mycoplasma pneumoniae. This manuscript describes the Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007, with a focus on pneumonia.

Key words appropriate use of antimicrobials, causative microorganism, children, guidelines, respiratory infections.

The Guidelines for the Management of Respiratory Infectious Diseases in Children were developed by members of the Japanese Society of Pediatric Pulmonology and the Japanese Society for Pediatric Infectious Diseases to facilitate proper management primarily for pneumonia and other childhood respiratory infections. The first edition1 was issued in 2004, and a revised edition2 was released in 2007.

The causative microorganisms of bronchopulmonary infections in children have not been sufficiently examined and assessed either in Japan or in other countries. The Guidelines were developed to recommend the appropriate use of antimicrobials for treating respiratory infections based on identification of the causative microorganisms. The Guidelines were the first pediatric guidelines in the world to utilize sputum cultures and other clinical specimens from infection sites to identify causative microorganisms. Clinical research has scrutinized the appropriateness of the recommendations in the Guidelines, and it is hoped that such scrutiny can improve the appropriateness of the recommended use of antimicrobials in childhood respiratory infections. This manuscript focuses on pneumonia, which is addressed in the 150-page Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007 that is used in clinical practice in Japan.

Principles for the development of Guidelines for the Management of Respiratory Infections in Children

The Guidelines were created with the objectives of: (i) improving the quality of the management and treatment of childhood respiratory infections; and (ii) considering antimicrobial treatment that minimizes the advent of drug-resistant pathogens. The Guidelines, which cover childhood respiratory infections, were developed in consideration of age-specific and other characteristics of children. The Guidelines are subject to revision when necessitated by trends associated with causative microorganisms, the emergence of resistant pathogens, the occurrence of adverse events, and the development of new drugs. The revised 2007 edition makes more information available about viral infections,
addresses pneumonia in children with underlying diseases and nosocomial pneumonia, and includes tuberculosis and measles in the scope of the Guidelines.

Classification of childhood respiratory infections and content of the Guidelines (Table 1)

Causative microorganisms of childhood respiratory infections and their detection

Bacteria

1 The problem of identifying the causative pathogens of respiratory infections:1,2 Identifying the causative bacteria of respiratory infections is more difficult than for other infectious diseases. Deep respiratory infections do not allow non-invasive collection of specimens from the affected site; and bronchopulmonary secretions are unavoidably contaminated by upper respiratory tract and oral flora on expectoration. Thus, isolating bacteria from these clinical specimens is not a reliable method for identifying the causative microorganism(s).

2 Upper respiratory tract flora: The detection of pharyngeal flora and percentage of bacterial colonies in healthy, symptom-free children differ in neonates, infants, preschool children, and school children. Streptococcus pneumoniae and Haemophilus influenzae are more frequently isolated and accounts for a greater percentage of colonies in infants and preschool children than in other age groups (Fig. 1).

3 Causative bacteria of childhood respiratory infections by disease location: Table 2 lists causative pathogens based primarily on data from the Department of Pediatrics of Chiba University and associated medical institutions.

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Appendix

Table 2: Contact details for organizations supporting the national stockpile of vaccines and antitoxins

Appendix

Table 1: List of reagents for rapid diagnosis of pathogenic microorganisms

Table 2: Contact details for organizations supporting the national stockpile of vaccines and antitoxins

Fig. 1  Distribution of bacteria by age group in throat cultures from healthy children (average % of colonies). *M. catarrhalis not classified. GNR, gram-negative rods. (Reproduced from The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007, Uehara and Sunakawa [eds.]* with permission.)

© 2011 The Authors
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Acute bronchiolitis
Acute epiglottitis
Acute laryngitis (croup)
Acute pharyngotonsillitis
Pyothorax
Pleurisy
Lung abscess
Pleural effusion
Pyothorax

<table>
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<th>Group A Streptococcus</th>
<th>Group B Streptococcus</th>
<th>Strep. viridans</th>
<th>Strep. pneumoniae</th>
<th>Staph. aureus</th>
<th>Corynebacterium diphtheriae</th>
<th>Moraxella catarrhalis</th>
<th>Haemophilus influenzae</th>
<th>Bordetella pertussis</th>
<th>Pseudomonas aeruginosa</th>
<th>Klebsiella</th>
<th>Anaerobic bacteria</th>
<th>Mycobacterium tuberculosis</th>
<th>Nocardia</th>
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○●△: frequency of occurrence from high to low.

4 Causative bacteria of upper respiratory infections and their detection: The Guidelines describe detection methods for Group A Streptococcus (GAS), including rapid diagnostics, and for Corynebacterium diphtheriae.

5 Causative bacteria of bronchopulmonary infections and their detection: The major bacteria responsible for childhood bronchopulmonary infections are S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus. These organisms are isolated with blood agar medium and chocolate agar medium. The clinical laboratory should be contacted in advance about suspected cases of pertussis and Legionella infections, which require specialized media for isolation.

6 Selection and determination of causative bacteria of bronchopulmonary infections: As previously stated, contamination with bacteria from the upper respiratory tract is a problem when diagnosing the causative bacteria for bronchitis, pneumonia, and other bronchopulmonary infections. Clinical specimens for culturing the causative bacteria for pneumonia as proposed by Moffet are presented in Table 3. Sputum and nasopharyngeal and throat secretions are categorized as being of dubious value for diagnosing the causative bacteria of pneumonia. Moffet states that bacteria cultured from blood, pleural fluid, and lung puncture are definitive. Blood culture is less sensitive than culture from lung puncture. Surveys conducted by Uehara of the causative bacteria determined from blood, pleural fluid, and lung puncture at pediatric training hospitals throughout Japan showed that the number of cases caused by S. aureus became fewer and those caused by S. pneumoniae and H. influenzae increased, beginning in the 1990s (Fig. 2). It must be noted that only a small number of the total cases were confirmed by these conclusive culture sources.

Pneumonia is transmitted via the airways as well as the bloodstream. We were able to raise the significance of sputum from “3. Cultures of dubious significance”, which included sputum and nasopharyngeal and throat secretions to “2. Occasionally significant culture sources”.

7 Assessment of causative bacteria identified in sputum culture: As sputum consists of bronchopulmonary secretions covered by upper respiratory secretions, it is difficult to differentiate bacteria of bronchopulmonary origin and those of upper respiratory tract when it is cultured as is. Washed sputum culture and quantitative culture are used to detect the true causative bacteria of bronchopulmonary infections. In washed sputum culture, a sputum specimen is washed with sterile saline solution, airway secretions thought to originate from the lower airway based on cytological evidence are cultured, and the predominant bacterium as determined semi-quantitatively is considered as the causative bacterium.

Table 3 Clinical specimens for identifying causative bacteria for pneumonia (created with modification from Moffet)

1. Conclusive Culture Sources
   - Blood
   - Pleural fluid
   - Lung puncture

2. Occasionally Significant Culture Sources
   - Transtracheal aspiration
   - Tracheotomy aspiration
   - Bronchoscopy aspiration
   (washed sputum)

3. Cultures of Dubious Significance
   - Sputum
   - Throat
   - Nose/nasopharynx
Pathogenic respiratory bacteria are predominantly isolated from purulent sputum and are often the likely causative bacterium. However, if the sputum is viscous, the isolated species may be from the oral flora. Broad classification of the causative bacterium can be made by Gram staining of sputum. The classifications defined by Geckler et al. are used for the quality control of sputum. Sputum is Gram-stained and observed under weak magnification (×100). Evaluation is based on squamous epithelial cells and neutrophil counts. The predominant organism detected in a Gram-stained smear of a washed sputum culture is of greater significance as the likely causative bacterium of a bronchopulmonary infection when found in close contact with alveolar macrophages (Fig. 3).

Table 4 lists criteria for determining causative bacteria. For *M. catarrhalis* to be confirmed as the causative species, the bacterium must be the predominant species in sputum culture and detected in macrophages by sputum cytology.

Sputum collection in infants and children is shown in Figure 4. Sputum collection should be attempted when the patient has a productive cough. If the patient is able to expectorate sputum, they should be instructed to discharge sputum into a sterile Petri dish with saline without contaminating the specimen by further productions of saliva, as far as possible. If the patient is an infant or preschool child who is unable to expectorate, the tongue should be depressed using a tongue depressor with a lamp to induce coughing. When the patient expectorates into the throat, a sterile swab should be promptly swiped around the sputum and placed in sterile saline. Recently, 1-mL disposable syringes have been used to aspirate specimens.

The value of sputum washing and nasopharyngeal and pharyngeal culture: Figure 5 shows the results of simultaneous culturing washed sputum, non-washed sputum, and nasopharyngeal and pharyngeal secretions for cases in which the causative bacteria was detected predominantly in washed sputum samples. Washed sputum samples showed better results than non-washed sputum samples. In the same patients, nasopharyngeal swabs showed better results than pharyngeal swabs, though detection was lower than in non-washed sputum samples. Direct culturing of sputum

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<th>Year</th>
<th>Pathogen(s)</th>
<th>Remarks</th>
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<td>1984-1986</td>
<td><em>S. aureus</em></td>
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<tr>
<td>1993-1994</td>
<td><em>S. pneumoniae</em></td>
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<td><em>H. influenzae</em></td>
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<tr>
<td>2000.8-01.12</td>
<td><em>GAS, GBS</em></td>
<td><img src="image4" alt="Graph" /></td>
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Table 4 Criteria for determination of causative bacteria in bronchopulmonary infection (adapted from Uehara with permission)

1. Pathogens occupying more than half of the colonies in culture or presenting >10^7 cfu/mL of washed sputum were regarded as “dominant”.
2. The same dominant pathogens were grown by repeated cultures.
3. The pathogens were seen perilveorally in smeared specimens.
4. Heavier growth of pathogens was observed with washed sputum than with nasopharyngeal or throat swabs.
5. The pathogens in washed sputum correlated with the clinical course of the disease: signs and symptoms, acute phase reactants, and especially the purulence (neutrophilia) of the sputum.
(non-washed) results in inferior identification of causative bacteria, as it is covered with bacteria from upper airway secretions. Sputum specimens should be pretreated to remove contamination from the upper airway as completely as possible before culturing. Use of nasopharyngeal and pharyngeal cultures is only of limited value in etiological diagnosis of bronchopulmonary infections. Nasopharyngeal culture should therefore be conducted when sputum cannot be collected. Nasopharyngeal culture, however, should be used to postulate rather than definitively identify the bacterium responsible for pneumonia.

Detection of bacterial antigens in urine: Pneumococcal antigen may show false-positive results in urine because of the high prevalence of *S. pneumoniae* in the upper respiratory tract of children.12 Urinary antigens are of excellent value in diagnosing legionellosis. Urinary antigen testing for *Legionella* spp. should be performed as a precaution in the critical cases of pneumonia.

**Fig. 4** Placement of instruments for the collection of sputum from pediatric patients.

**Fig. 5** Simultaneous culturing of washed and non-washed sputum specimens and nasopharyngeal and pharyngeal swabs from cases in which causative bacteria could be identified from washed sputum cultures. (Reproduced from Takeda et al.,11 with permission.)

10 Blood culture: Although sensitivity is not as high as other methods, blood cultures are of extreme value in selecting drugs for treatment when identifying the causative pathogen. Blood culture should be conducted whenever possible. Blood culture is discussed in detail in *Cumitech 1C: Blood Cultures IV*, a publication of the American Society for Microbiology.13

**Mycoplasma, Chlamydia**

*Mycoplasma pneumoniae* and *Chlamydia* infections are diagnosed by: (i) confirming significantly elevated or abnormally high serum antibody titers; and (ii) performing isolation culture, antigen detection, and nucleic acid detection on specimens from the infection site.

1 *Mycoplasma: M. pneumoniae* is the only significant pathogen involved in childhood respiratory infections. *Mycoplasma* infections are diagnosed by detection of *Mycoplasma* from the infection site and confirmation of increased antibody titers. *Mycoplasma* is detected in nasopharyngeal swab specimens, sputum, and pleural fluid. Detection is accomplished with direct fluorescent antibody assay, isolation culture, enzyme immunoassay, DNA probe assay, polymerase chain reaction (PCR), and other methods. Liquid pleuropneumonia-like organism (PPLO) media and other special media are used for isolation culture, which typically requires at least 7 days. PCR features excellent sensitivity and specificity. Serological diagnosis is accomplished with methods including particle agglutination (PA), cold agglutinin titer, complement fixation, indirect hemagglutination assay, and enzyme immunoassay.14 Although serum antibody titer is at least fourfold higher in the acute and convalescent phases, increased immunoglobulin (Ig)M antibody levels must be identified to reach a definitive diagnosis. Infection may be strongly suspected if a PA titer of at least 320 or a complement fixation titer of at least 64 is detected in single serum. Infections in infants show poor antibody response.

2 *Chlamydia: The three species Chlamydophila pneumoniae, Chlamydophila psittaci, and Chlamydia trachomatis are the causes of childhood Chlamydia respiratory infections. Chlamydia* infections are diagnosed by detection of *Chlamydia* from...
the infection site and confirmation of significantly increased antibody titer. *Chlamydia* is detected in nasopharyngeal swab specimens, sputum, and pleural fluid. Direct fluorescent antibody, enzyme immunoassay, PCR, and other techniques are used for detection. Isolation culture in cell culture requires at least 7 days. PCR offers good sensitivity and specificity. The Committee on Serological Diagnosis of *Chlamydia pneumoniae* infection (chaired by Toshio Kishimoto) sets related diagnostic standards in Japan.\(^{15}\)

Although serum antibody titer is at least fourfold higher in the acute and convalescent phases, increased IgM antibody levels must be identified to achieve serological diagnosis. For initial infections, a diagnosis can be reached in a relatively early stage using IgM antibody assay. Infections in infants show poor antibody response.

It should be noted that legionellosis is attributable to aspiration of *Legionella pneumophila* and other *Legionella* spp. from water coolers and other climate-control equipment. Only a few infants have acquired legionellosis in a neonatal intensive care unit. Legionellosis is more often diagnosed through rapid antigen diagnostics of urine specimens (61%) than it is from serum antibody titers. Rapid antigen diagnostics should therefore be attempted in cases of critical pneumonia. Isolation culture requires special media (B-CYE medium, World Health Organization [WHO] agar medium).

**Viruses**

The characteristics of the viruses often isolated in childhood respiratory tract infections differ according to the infection site. Determining causative microorganisms according to symptoms alone is often difficult. The flow of testing is presented in the original Guidelines.

Medical staff collecting specimens for testing must be careful to perform collection at initial presentation in the early stage of the disease and to place specimens in a preserving solution for specimens for isolation (such as those designated by testing facilities). Specimens should be stored at low temperature (often \(4^\circ\)C). Specimens should be promptly shipped refrigerated to the testing facility. Serum specimens must be collected as paired sera once during the acute phase and again during the convalescent phase, 14–21 days after onset. A definitive diagnosis is reached when antibody titer is increased at least fourfold. The microplate method used by Numazaki *et al.* at the Virus Research Center of Sendai National Hospital\(^{16}\) is well suited for the co-detection of viruses, is recommended by the WHO, and is increasingly used at Prefectural Institutes of Public Health in Japan, but the method is not feasible in all cases and must be selected according to the reason for culturing. The 2007 Guidelines refined the list of rapid diagnostic testing, isolation culturing, nucleic acid detection testing, and serological detection methods for influenza virus, respiratory syncytial virus (RSV), and adenovirus pathogens.

**Testing for rapid diagnosis of childhood respiratory infections**

The Guidelines summarize: (i) trends in testing for the rapid diagnosis of childhood respiratory infections; (ii) the strengths and limits of immunochromatography; (iii) reagents for blood assay for *Mycobacterium tuberculosis* (BAMT), including whole-blood interferon-\(\gamma\) assay for diagnosing tuberculosis; and (iv) points to consider when performing rapid diagnostic testing.

**Upper respiratory infections**

1 **Common cold (nasopharyngitis):** Colds, which are caused primarily by viruses, are not treatable with antimicrobials. Antimicrobials fail to improve the course or prognosis of colds and have been found not to protect against lower respiratory tract infections. Fever alone with no respiratory symptoms is differentiated based on the presence of occult bacteremia, urinary tract infections, and other conditions.

2 **Pharyngitis/tonsillitis:** These conditions are often of viral origin. Antimicrobial treatment is indicated for primarily GAS infections. The Guidelines now recommend penicillin (PC)-based antimicrobials\(^{17}\) as first-line treatments for GAS based on the discussions of GAS treatment that have taken place since 2004, but also list cephem antimicrobials for short-term therapy. Cephem or macrolide antimicrobials are recommended for children with penicillin allergies, but some children are also allergic to cephem antimicrobials. Not a few GAS isolates in Japan show resistance to macrolide antimicrobials, making cross-resistance a concern.

3 **Croup syndrome**

   1. Viral croup: Viral croup is to be treated symptomatically. Dexamethasone therapy is an option for severe cases.
   2. Acute epiglottitis: The course of this serious disease can include asphyxiation occurring 10 h after onset. A tongue depressor must not be used. Securing the airway is an urgent priority. Lateral radiography of the neck can show any epiglottic enlargement. *H. influenzae* type b (Hib) is the causative microorganism in \(\geq 90\%\) of all cases. The disease is treated with the antimicrobials: ceftriaxone, cefotaxime, meropenem, or tazobactam/piperacillin. Now that the Hib vaccine (approved in January 2007 in Japan) has been found to be safe and effective, Hib epiglottitis can be almost completely prevented through vaccination.\(^{18}\)
   3. Laryngeal diphtheria: Although very rare (only one case has been officially reported over the past several years), the possibility of laryngeal diphtheria must be kept in mind in unvaccinated and older children. Antitoxin therapy should be administered first and foremost.
   4. Bacterial tracheitis: Although very rare, bacterial tracheitis can cause asphyxiation. *S. aureus* and other organisms cause this disease.

**Bronchitis**

1 **Acute bronchitis:**\(^{19}\) Although acute bronchitis is usually viral, oral antimicrobials (consistent with those used for pneumonia) are used when bacterial bronchitis (*H. influenzae, S. pneumoniae*) is suspected based on fever, productive cough, or purulent sputum.

2 **Protracted bronchitis (protracted, recurrent, and chronic bronchitis):**\(^{7}\) If infection is confirmed, the causative bacteria (*H.
influenzae > Streptococcus pneumoniae) should be identified from the sputum and treated with the appropriate antimicrobial(s). Any underlying diseases (e.g. sinusitis, immunodeficiency) must be identified and superinfection by Pseudomonas aeruginosa or other organisms must be avoided.

Bronchiolitis

Acute bronchiolitis is common in infants and is primarily caused by RSV (45–75%). Fever infrequently exceeds 38.5°C, and chest radiography often shows hyperinflated lungs. Some serious cases in infants under 3 months old require respiratory management. Antigen testing is useful. Some infections are caused by the human metapneumovirus, which has become a recent focus of attention. No consensus has been reached on the value of PCR detection of the human bocavirus. Palivizumab is an effective prophylactic for RSV infection in high-risk infants.

Pneumonia

1 The definition of pneumonia: This acute respiratory infection is characterized by fever, rhinorrhea, and cough. Chest radiography, computed tomography (CT), and other imaging modalities show acute new infiltration in the lungs. Adventitious breath sounds and decreased respiratory sounds on chest auscultation can be observed in pneumonia.

2 Diagnosis of pneumonia: Patients suffering primarily from fever, cough, and dyspnea and who are suspected of having pneumonia based on chest findings should undergo chest radiography. Viral and Mycoplasma pneumonia are characterized primarily by interstitial lesions, and may show no abnormalities on chest auscultation. Once a definitive diagnosis of pneumonia is made based on imaging, the causative microorganisms should be identified in the blood and sputum (or in nasopharyngeal secretions). The need for antimicrobial(s) is determined in reference to pulmonary radiographs, acute phase reactants, and in consideration of the presumed causative microorganism. It must be remembered that infants and preschool children often cannot report dyspnea. When evaluating severity, features to check in addition to chest imaging include tachypnea (≥50 breaths/minute in children 1 year old and younger and ≥40 breaths/minute in children aged 2–5 years old) and retractions, nasal alar breathing, shoulder breathing, grunting, and cyanosis as signs of dyspnea (discussed later).

3 Causative microorganisms and examination

(1) Incidence of causative microorganisms: Based on the limited number of pneumonia cases for which the causative bacterium was confirmed through blood or pleural fluid culture in a nation-wide survey, the incidence of infections caused by S. pneumoniae and H. influenzae have exceeded those caused by S. aureus since the 1990s (Fig. 2). Trends in S. aureus infection must be monitored.

Of the washed sputum cultures from bronchopulmonary infections, predominant bacteria were identified in about 30% of cases, and recent trends show that H. influenzae became more common than S. pneumoniae, and M. catarrhalis, in that order. S. pneumoniae pneumonia has been increasing since 1995 and accounted for about 30% of cases in which a causative organism was identified in 2005 (Fig. 6). For cases in which the causative pathogen of pneumonia was identified by washed sputum culture, about 30% of cases were attributed to bacterial pneumonia, 10–20% were attributed to M. pneumoniae, about 20% were viral, and the cause of the remaining 30% could not be determined. Trends in causative pathogens identified in washed sputum culture at three medical institutions associated with Chiba University showed H. influenzae and S. pneumoniae to be the major culprits since 1965, with some cases attributed to M. catarrhalis.

(2) Causative microorganisms and age distribution: The Guidelines summarize evidence about the age distributions associated with the causative microorganisms of pneumonia from the publication of McIntosh. The Japanese evidence is similar. Although C. pneumoniae is well characterized, the data on other microorganisms do not differ substantially from those listed in medical texts, and no frequencies are stated. An investigation of the relationship of age in childhood pneumonia at Chiba Kaihin Municipal Hospital (1998–99) showed that of the 634 cases of childhood pneumonia treated, 170 (26.8%) were in 1-year-old children, 115 (18.1%) were in 2-year-old children, and 84 (13.2%) were in 4- to 11-month-old infants. A total of 512 (80.8%) were in children 4 years old and younger. Bacterial pneumonia was confirmed in washed sputum culture in 163 cases (25.7%). All cases were attributable to H. influenzae, S. pneumoniae, or combinations of these two, with the exception of three cases caused by M. catarrhalis, one caused by Bordetella pertussis, and two caused by GAS. Pneumonia was more commonly of bacterial origin in the younger age groups of hospitalized patients at Chiba Children’s Hospital, while the incidence of Mycoplasma pneumonia increased with age (Fig. 7).

Although C. pneumoniae infections are relatively common beginning at young ages outside Japan, the prevalence of C. pneumoniae IgG antibody in Japanese children increases with age starting with an increased prevalence in 4–7-year-olds, a sharp increase to 44% in 8–11-year-olds, and about 50% above the age of 11 years. The data provided by Kishimoto on antibody incidence similarly indicate an increase in prevalence beginning at 6 years old. Grayston, who stated that the incidences of bronchitis and pneumonia are about equal from 5 to 9 years old and that pneumonia is more common from 10 years old, reported that most cases of pneumonia are attributed to C. pneumoniae in older children.

4 Clinical symptoms, laboratory test findings, and antimicrobial selection

(1) Clinical symptoms and physical findings encountered with different causative pathogens: Investigation of many
Fig. 6  Trends in causative bacteria in childhood bronchopulmonary infections based on washed sputum culture (percentages among cases of known pathogens). MC, Moraxella catarrhalis; Pn, pneumococcus. (Prepared from data provided by Dr. Kurosaki of Chiba Municipal Kaihin Hospital; reproduced from The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007, Uehara and Sunakawa [eds.] with permission.)

Fig. 7  Causative bacteria of community-acquired pneumonia in children. (Data collected October 1988–March 2002 by A. Nakamura of Chiba Children’s Hospital; reproduced from The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007, Uehara and Sunakawa [eds.] with permission.)
cases in which the causative pathogen has been identified has revealed that bacterial pneumonia often involves productive cough and that *M. pneumoniae* disease often lacks labored breathing and abnormalities on auscultation. *C. pneumoniae* infections result in low-grade fever and prolonged coughing. Diagnostics for causative organisms, however, are required because postulating the causative microorganism according to symptoms is difficult in individual patients.26,27

(2) Causative microorganisms and laboratory test findings on admission: Bacterial and viral pneumonia had been considered distinguishable by the intensity of the inflammatory response. In blood culture-negative bacterial pneumonia, although white blood cell counts, C-reactive protein levels, and erythrocyte sedimentation rates were significantly different from those of viral pneumonia (*P* < 0.01), overlap is seen in about one-third of patients, making differentiation of cause impossible in individual cases.27 Bacterial culture is therefore necessary before antimicrobial treatment. The possibility of *Mycoplasma pneumoniae* should be considered when C-reactive protein levels and erythrocyte sedimentation rates are high, but white blood cell counts are not elevated.

(3) Causative pathogens and findings from chest radiography: The cause of pneumonia cannot be clearly differentiated based on chest radiography performed on admission using the differentiation methods of Swischuk and Hayden28 or the scoring method of Khamapirad and Glezen.29

(4) Classifications of pneumonia severity: Tachypnea: The WHO established management criteria for pneumonia in developing countries, with a focus on tachypnea and labored breathing. Kurosaki27 compared respiratory rates (≥250 breaths/minute in children 1 year old and younger and ≥40 breaths/minute in children under 5 years old) to findings from washed sputum cultures and reported that tachypnea can be used as an index for determining the appropriateness of antimicrobial treatment before culture results become available for 1–4-year-old children.30 Assessing the severity of pneumonia is a first step toward determining whether the patient should be treated as an outpatient or admitted, whether antimicrobials should be administered, and whether oral or intravenous (i.v.) administration is appropriate. Criteria for assessing pneumonia severity are shown in Table 5.

(5) Hospitalization eligibility criteria: Patients with a severity classification of mild should be treated on an outpatient basis, while patients with moderate or severe infections should be admitted for treatment.

(6) Important factors when considering initial antimicrobial therapy

(i) Intensity of bacterial pathogenicity: *S. pneumoniae* has the strongest pathogenicity of the three causative organisms of bronchopulmonary infections: *S. pneumoniae, H. influenzae* and *M. catarrhalis*. Antimicrobial therapy that considers *S. aureus* is occasionally recommended for infants and children with underlying diseases.

(ii) Relationship between age and causative organism: The organisms primarily responsible for pneumonia differ with age of children as follows.

- **Neonates**: Group B Streptococcus, *Escherichia coli*, and other intestinal flora.
- **Infants to children aged 5 years old**: viruses, *H. influenzae*, and *S. pneumoniae*.
- **Children 6 years of age and older**: *M. pneumoniae, C. pneumoniae, H. influenzae*, and *S. pneumoniae*.

Macrolide antibiotics should be considered first in children at least 6 years old who do not exhibit productive cough.

(iii) Pharmacokinetics of oral antibiotics: The pharmacokinetics-pharmacodynamics (PK-PD)
theory indicates that new cephem antibiotics, when recommended, should be administered at a high dose.

(iv) Minimizing drug resistance: Care must be taken to use antibiotics appropriately (particularly oral cephem antibiotics).

(v) Synthetic penicillin therapy for *S. pneumoniae* and *H. influenzae*: The Drug-Resistant Streptococcus pneumoniae (DRSP) Therapeutic Working Group of the Centers for Disease Control and Prevention of the USA, reasoning that pneumonia in children under 5 years of age is often bacterial in origin, advocates a β-lactam antibiotic (amoxicillin, amoxicillin/clavulanic acid, or cefuroxime for outpatient cases) for the initial treatment of pneumonia.33,34 We set dosages for the treatment of cases for which *S. pneumoniae* was the predominant organism isolated from washed sputum based on the breakpoint for i.v. ampicillin defined by the Japanese Society of Chemotherapy of 2 μg/mL. Treatment with oral amoxicillin (30–40 mg/kg/day) and i.v. ampicillin (80–150 mg/kg/day) showed no significant differences for pneumonia with the following: penicillin-susceptible *S. pneumoniae* (PSSP), penicillin-intermediate resistant *S. pneumoniae* (PISP), and penicillin-resistant *S. pneumoniae* (PRSP).32 (Note: The 2007 edition of the Guidelines lists penicillin G [PcG] resistance criteria that were revised in 2008. Following are the criteria in the 2007 edition of the Guidelines: PSSP, PcG-MIC ≤ 0.06 μg/mL; PISP, PcG-MIC, 0.12–1 μg/mL; and PRSP, PcG-MIC ≥ 2 μg/mL). The *H. influenzae* ampicillin resistance criteria of the Clinical Laboratory Standards Institute (CLSI) of the USA35 defines sensitivity as ≤1 μg/mL, moderate resistance as 2 μg/mL, and resistance as ≥4 μg/mL by the broth microdilution method. Most broncho-pulmonary infections caused by β-lactamase-non-producing ampicillin-resistant (BLNAR) strains in Japan are treatable with i.v. ampicillin. Piperacillin, cefotaxime, and ceftriaxone offer reliable antibiotic activity against BLNAR strains. The response rate to piperacillin was 95%.34 There are few patients with pathology caused by β-lactamase-producing *H. influenzae* strains that have shown clinical deterioration when treatment is initiated with oral amoxicillin or i.v. ampicillin. There is still time to switch antibiotics if resistance is identified after treatment is initiated.

(vi) Synthetic penicillin therapy for *M. catarrhalis*: Synthetic penicillin is clinically effective in treating *M. catarrhalis* infections even though the microorganism produces β-lactamase and is bacteriologically resistant to amoxicillin35,36 because the produced β-lactamase has low activity.

(vii) Penicillin-binding protein (PBP) mutations: PBP of *S. pneumoniae* readily mutate in the presence of cephem antibiotics.37 Mutation leads to increased resistance to β-lactam antibiotics and consequently DRSP strains. PBP mutations also underlie BLNAR and β-lactamase-producing amoxicillin-clavulanate resistant (BLPACR) *H. influenzae* strains. The increase in the prevalence of BLNAR strains is attributable to the widespread use of oral cephem antibiotics, which reaches a concentration that is only a fraction of that of amoxicillin.37

(7) Initial antimicrobial therapy when etiological pathogen is unknown: Antimicrobial agents recommended for initial treatment when the pathogen is unknown are shown for different age groups and for hospitalized patients and outpatients in Table 6. Agreement has been reached on the appropriateness of the selections of initial antimicrobial agents given in the 2004 edition of the Guidelines. These selections must be continuously evaluated to take trends in causative microorganisms and drug resistance into account.

(8) Selection of antimicrobial agents when the etiological pathogen of pneumonia is known: monotherapy as a starting point: When the pathogen responsible for the pneumonia is known, the antimicrobial agent is selected in consideration of drug susceptibility and pharmacokinetics. Macrolide-resistant *Mycoplasma* strains have been increasing since 2000 (this is discussed later).

(9) Assessment of antimicrobial agent efficacy and duration of use: Antimicrobial agents for treating community-acquired pneumonia are normally sufficiently effective when administered for 3 to 7 days. Efficacy is assessed after 2 or 3 days (48–72 h after start of administration). Efficacy should be initially assessed after 2 days in younger children and severe cases. Assessment is performed to determine whether the initial antimicrobial agent is effective and whether the drug should be continued or switched. The duration of use will vary among individual patients. For common bacteria, use can be discontinued 3 days after the patient’s fever breaks. A longer duration is required for *S. aureus* pneumonia. For *Mycoplasma* and *Chlamydia* infections, 10 days of new macrolide (clarithromycin) treatment or 3 days of azithromycin treatment (5 days in the USA) is recommended.

(10) Actions to take and selections to make when no response is achieved

(i) Actions to take when the patient does not respond to antimicrobial therapy: The correctness of the pneumonia diagnosis and the possibility of another disease producing pneumonia-like findings on imaging should be considered in order to distinguish pneumonia cases due to causative microorganisms other than common causative bacteria, such as viruses, tuberculosis, and fungi.
Selection of antimicrobials when the patient does not respond to antimicrobial therapy:

- If a β-lactam antibiotic was initially used: Pneumonia is often caused by *H. influenzae* and *S. pneumoniae*, against which ampicillin and amoxicillin are recommended. These drugs are reportedly effective even against BLNAR and PRSP.

- For mild and moderate non-responsive cases, *Mycoplasma* or *Chlamydia* infection should be suspected, and the initial antimicrobial agent should be switched to or used in combination with a macrolide. A broad-spectrum i.v. cephem antibiotic or i.v. carbapenem antibiotic should be used when response is insufficient. For rapidly progressive, severe cases and critical cases, a carbapenem antibiotic and macrolide antibiotic should be used in combination. Addition of an anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agent is to be considered.

- If a macrolide antibiotic was initially used: Treatment should be switched to a β-lactam antibiotic to treat macrolide-resistant *S. pneumoniae* and *H. influenzae*. Treatment should be switched to the optimal antimicrobial agent once the causative pathogen is identified. When the condition of the patient is good and a *Mycoplasma* infection is suspected, switching to a tetracycline antibiotic should be considered to treat possible macrolide-resistant *Mycoplasma* infection.

(ii) Outpatient parenteral antimicrobial therapy (OPAT):

OPAT is sometimes used to treat patients with moderate pneumonia who are unable to be admitted. Such patients must visit the medical institution daily and be carefully monitored. Once-daily ceftriaxone has a long half-life and is commonly used. A first-line treatment for bacterial meningitis, ceftriaxone should not be used readily and widely until the Hib vaccine has substantially reduced the prevalence of meningitis.

### Table 6

<table>
<thead>
<tr>
<th>Severity</th>
<th>2 months to 5 years old<em>1</em>2<em>4</em>5</th>
<th>≥6 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>AMPC ± CVA or SBTPC p.o.</td>
<td>Macrolide p.o.</td>
</tr>
<tr>
<td></td>
<td>or Broad-spectrum cephem p.o.*3</td>
<td>or Tetracycline p.o.*4</td>
</tr>
<tr>
<td><strong>Inpatient</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to Severe</td>
<td>ABPC ± SBT i.v. or PIPC i.v.</td>
<td>ABPC ± SBT i.v. or PIPC i.v.*2</td>
</tr>
<tr>
<td></td>
<td>or Broad-spectrum cephem i.v.*3</td>
<td>or Broad-spectrum cephem i.v.*4</td>
</tr>
<tr>
<td><strong>Critical</strong></td>
<td>Carbapenem d.i.v. ± Macrolide p.o./d.i.v.*6</td>
<td></td>
</tr>
</tbody>
</table>

When the causative pathogen has been identified, change to the appropriate antimicrobial agent.

*1: With concomitant macrolide when *Chlamydia trachomatis* infection is identified.

*2: With concomitant macrolide when *Mycoplasma/Chlamydophila pneumoniae* infection is strongly suspected.

*3: The following offer superior antibacterial activity against *S. pneumoniae* and *H. influenzae*: Representative oral drugs: CDTR-PI; CFPN-PI; CFTM-PI. Representative intravenous drugs: CTRX; CTX.

*4: Use in children <8 years old only when other agents are ineffective or cannot be used.

*5: In principal, children <1 year old are hospitalized.

*6: With concomitant macrolide when Legionella cannot be ruled out.

AMPC, amoxicillin; CDTR-PI, cefditoren pivoxil; CFPN-PI, cefcapene pivoxil; CFTM-PI, cefteram pivoxil; CTRX, ceftriaxone; CTX, cefotaxime; CVA, clavulanic acid; d.i.v., drip intravenous; i.v., intravenous; PIPC, piperacillin; p.o., per os; SBTPC, sultamicillin.

### Pleurisy and pyothorax

Although pyothorax prevalence in Japan has decreased with the waning incidence of *S. aureus* pneumonia, vigilance is required because the disease is still on the increase in countries outside Japan, despite widespread use of the pneumococcal conjugate vaccine.

### Pneumonia in patients with underlying diseases

The 2007 edition discusses pneumonia with accompanying underlying conditions (blood diseases, immunodeficiency, neonates, and cardiac diseases).

### Nosocomial pneumonia

Nosocomial pneumonia is defined as pneumonia acquired after a hospital stay of at least 48 h. Measures must be taken to prevent children from becoming infected due to the hospital environment and medical acts (including those leading to ventilator-associated pneumonia) as well as from other patients, attendants, visitors, and medical personnel. The Guidelines present measures for preventing respiratory infections acquired through different routes and discuss the person-to-person transmission of respiratory infections. The Guidelines also recommend the vaccination of medical personnel.
Main diseases controlled by vaccination

The Guidelines discuss influenza, measles, pertussis, diphtheria, and tuberculosis. Also proposed are draft diagnostic criteria for pertussis based on epidemiological data that factor in the relative increase in the disease among older children and adolescents and DTP-vaccinated children and adults. Although affected older children and adults exhibit prolonged and severe coughing, no characteristic symptoms can be identified in children without a detailed interview. The disease lacks elevated white blood cell and lymphocyte counts. A novel trivalent vaccine for adolescents and adults (Tdap) has been developed in Europe and the USA.

Pathogen resistance in community-acquired childhood respiratory infections

A classification system for S. pneumoniae and H. influenzae based on the analysis of antibiotic resistance genes is presented. Antimicrobial agents currently used to treat resistant pathogens are listed (note: the antimicrobial susceptibility of S. pneumoniae and H. influenzae is discussed in Ubukata3). Most strains with an ampicillin-MIC ≤ 2 μg/mL are treatable using amoxicillin or i.v. ampicillin, but when therapy must be changed, oral faroampicillin-MIC2 and adults (Tdap) has been developed in Europe and the USA.

and lymphocyte counts. A novel trivalent vaccine for adolescents detailed interview. The disease lacks elevated white blood cell characteristic symptoms can be identified in children without a increase in the disease among older children and adolescents and tuberculosis. Also proposed are draft diagnostic criteria for DTP-vaccinated children and adults. Although affected older children and adolescents and 4.3 days for resistant strains vs 1.4 days for susceptible strains), that for infections by susceptible strains (mean duration of fever: 4.3 days for resistant strains vs 1.4 days for susceptible strains), the clinical symptoms are not more severe. Changing treatment to a tetracycline antibiotic should be considered if fever persists for more than 48 h after macrolide antibiotic initiation.

The Guidelines for the Management of Respiratory Infectious Diseases in Children in Japan 2007 are summarized here with a focus on pneumonia. Only selected tables and figures to illustrate the Guidelines could be reproduced here due to limited space.

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NCCLS. Performance standards for antimicrobial susceptibility testing; eleventh informational supplement. MIC interpretive standards (µg/mL) for *Haemophilus* spp. 2001; **21**: 98–9, in NCCLS document M100-S11.


