

# UPDATES OF PEDIATRIC RESPIRATORY TRACT INFECTIONS

## Introduction to Guest Editor – Cheng-Hsun Chiu, MD, PhD

On behalf of the Chang Gung Medical Journal, I would like to express my thanks to Professor Cheng-Hsun Chiu for serving as the guest editor. The authors who have contributed articles to this special section “UPDATES OF PEDIATRIC RESPIRATORY TRACT INFECTIONS” are all outstanding experts in their fields.

Professor Cheng-Hsun Chiu graduated from Chung Shan Medical and Dental College in 1989 and completed his pediatric residency at Chang Gung Memorial Hospital in 1993. He earned his PhD from the Graduate Institute of Clinical Medicine of Chang Gung University in 1997 and received further postdoctoral fellowship in the Department of Pediatrics, University of British Columbia, Canada from 1997 to 1999.



Dr. Cheng-Hsun Chiu

Currently, Dr. Chiu serves as the professor and vice chairman of the department of pediatrics at Chang Gung Children's Hospital, Chang Gung Medical College and University. He is academically active with main research interests on pediatric infectious diseases and vaccine, bacterial pathogenesis, genetics and genomics. His most outstanding achievements include identifying that *Salmonella enterica* serotype Choleraesuis is resistant to ceftriaxone and ciprofloxacin, and sequencing the genome of *Salmonella enterica* serovar Choleraesuis. Those two works were published in Lancet and Nucleic Acids Research respectively. Up to now, he has contributed three book chapters, published 131 refereed papers and 38 conference papers in the fields of infectious diseases microbiology. He has been also invited as a guest speaker at the International Symposium on Antimicrobial Agents and Resistance in Korea, Malaysia and Taiwan. Professor Chiu is truly an eminent physician scientist in his professional field.

**Fu-Chan Wei, MD**  
**Editor-in-Chief**

# Community-Acquired Pneumonia in Children: From Diagnosis to Treatment

David Greenberg, MD; Eugene Leibovitz, MD

Community-acquired pneumonia (CAP) in children is a leading cause of childhood morbidity and mortality mainly in the developing world. Its etiology can be viral, bacterial, or mixed infection. The etiological agents are different in different age groups and during the various seasons of the year. Chest X-rays and inflammatory laboratory tests have low diagnostic sensitivity and specificity. CAP in children has an important impact on society and is a frequent cause of physician visits, work loss, and reduction of quality of life of the children and his/her family. The use of treatment algorithms in the developing countries has led to lower mortality rates, but the future of this approach, given the rate of development of antimicrobial resistance, is uncertain. The wider use of pneumococcal vaccines may represent an important advance in the prevention of pneumonia caused by *Streptococcus pneumoniae*. (*Chang Gung Med J* 2005;28:746-52)

**Key words:** community-acquired pneumonia, children.

Community-acquired pneumonia (CAP) is the leading cause of childhood morbidity and mortality in developing as well as in developed countries, resulting in an estimated number of 4 million deaths annually. The disease is most prevalent in children < 5 years of age, reaching an annual incidence of 34-40 cases/1000 children in Europe and North America.<sup>(1,2)</sup>

*Streptococcus pneumoniae* and *Haemophilus influenzae* type b are the most common causes of severe pneumonia in children. The successful introduction of *H. influenzae* type b conjugate vaccines over the past decade has largely eliminated invasive disease caused by this pathogen. As a result, *S. pneumoniae* is likely to be the most frequent cause of severe pneumonia in children immunized against *H. influenzae* type b.<sup>(3)</sup> However, a large number of microorganisms can cause childhood pneumonia and therefore determining the cause of the disease in an individual case may be difficult.

The diagnosis of pneumonia is based primarily on an algorithm built on patient's history, clinical signs and symptoms, laboratory tests and chest radiograph findings. Case definitions for pneumonia can vary by geographic region and even between various hospitals as a result of lack of standardized diagnosis criteria.<sup>(3,4)</sup>

Laboratory tests measuring the systemic inflammatory reaction associated with pneumonia are being used routinely in clinical practice but their sensitivity and specificity are relatively low. In addition, other diagnostic techniques such as measurement of bacterial antigens, antibodies, or immune complexes in blood or urine or bacterial DNA were developed but their diagnostic value is questionable.<sup>(5,6)</sup>

Management of CAP in children involves a number of therapeutic decisions including the major one whether to treat or not with antibiotics and also what is the choice of the appropriate antibiotic drug and its route of administration.<sup>(7,8)</sup>

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### Clinical Characteristic

Bacterial pediatric CAP, especially in cases due to *S. pneumoniae*, presents in its classical form as an acute illness with rigor, fever > 39°C, general malaise with productive cough, dyspnea and chest pain. The most common symptoms in children are fever and cough, which occur in 90% and 70% of all patients, respectively.<sup>(3,9)</sup> In some cases *S. pneumoniae* pneumonia can present with an atypical and incomplete course, presented as high fever and leukocytosis without respiratory symptoms.<sup>(10)</sup> Severe abdominal pain, with or without vomiting, may be the only presenting symptom, especially in left lower lobe pneumonia, due to enlarged mesenteric lymphadenopathy.<sup>(11)</sup> Irritation of the meninges in cases of upper lobe pneumonia may elicit meningeal signs without meningitis.<sup>(12)</sup>

Pleural effusion can be found in up to 40% of patients with pneumococcal pneumonia but in only 10% the fluid amount is considered sufficient to be aspirated and only about 2% have empyema.<sup>(13)</sup> These patients can present with friction rub, abdominal pain, chest pain and dullness at percussion. In patients with pleural effusion, fever can persist for longer duration than in patients with pneumonia without pleural effusion, despite adequate treatment.<sup>(9)</sup>

### Etiology of Pediatric Community-Acquired Pneumonia

Determining the cause of an individual case may be difficult.<sup>(14)</sup> Blood cultures are not routinely performed and have little value in areas where antibiotic use prior to seeking medical care is common. The lung itself is rarely sampled directly, and sputum representing lower-airway secretions can rarely be obtained from children.

Nasopharyngeal washes are a useful tool for the detection of respiratory viruses usually associated with pneumonia. Several studies of pediatric pneumonia have emphasized the importance of infections with respiratory viruses such as respiratory syncytial virus (RSV), influenza, parainfluenza, adenovirus or rhinoviruses in children.<sup>(3)</sup> *Mycoplasma pneumoniae* was found mainly in school-age children and in lower rate *Chlamydia pneumoniae*, 45-60% and 10-17%, respectively.<sup>(15)</sup>

The role of bacteria as a cause of severe pneumonia was best documented in lung-puncture stud-

ies, which confirmed the importance of *S. pneumoniae*, *Staphylococcus aureus* and *H. influenzae*, including nontypable strains, as causes of severe pneumonia.<sup>(16)</sup> An analysis of 59 studies that were published in 6 languages found that bacterial etiology can be detected in > 50% of cases. In these studies *S. pneumoniae* was isolation in cases of CAP varied widely from 3% to 100% of all culture positive.<sup>(17)</sup> In some studies, *Streptococcus pyogenes* and gram-negative enteric bacteria have also been isolated.<sup>(17)</sup>

### Laboratory Aspects

The value of blood cultures in pneumococcal pneumonia is little and can be positive in less than 1% of all cases.<sup>(18)</sup> Laboratory tests measuring the systemic inflammatory reaction associated with pneumonia such as white blood cell (WBC) count, absolute neutrophil count, erythrocyte sedimentation rate, C-reactive protein and procalcitonin are routinely used in clinical practice but their sensitivity and specificity are relatively low.

No differences were noted between lobar and interstitial pneumonia regarding the WBC and granulocytes. There were significant differences between bacteria and viral pneumonia in total WBC and neutrophil counts but there is a considerable overlap between these groups.<sup>(19)</sup>

Erythrocyte sedimentation rates (ESR) were found to be higher in patients with consolidation or lobar pneumonia than in patients with interstitial pneumonia. The differences between bacterial and viral pneumonia were demonstrated in several studies.<sup>(3,19-21)</sup>

C-Reactive Protein (CRP) levels were higher in patients with alveolar pneumonia than in patients with interstitial pneumonia. In addition, CRP levels were higher in children with bacterial pneumonia than in children with pneumonia of viral etiology. In children with pneumonia caused by *S. pneumoniae* CRP was found to be significantly higher than in those with non-pneumococcal pneumonia.<sup>(22,23)</sup>

Procalcitonin (PCT) demonstrated to be able to discriminate between case of bacterial and viral pneumonia despite some overlaps (mainly at the lower range). PCT values were significantly higher in children with *S. pneumoniae* bacteremia and pneumococcal pneumonia than in non-bacteremic and non-pneumococcal pneumonia cases. A cutoff of > 1mg/L was demonstrated as a good cut-off to distin-

guish between viral and bacteria pneumonia.<sup>(22,23)</sup>

Comparisons of different cutoffs for WBC, ESR, CRP and PCT showed increased specificity but low sensitivity in differentiating bacterial and viral pneumonias. PCT (> 1mg/L) is more discriminatory than WBC, CRP or IL-6 in differentiating between pneumonia caused by *S. pneumoniae* and viral pneumonia.<sup>(5,22,23)</sup>

Other diagnostic techniques such as measurement of bacterial antigens, nucleic acid (by PCR), antibodies, or immune complexes in blood or urine in patients with pneumonia were developed. Some of these methods may be available only in research facilities and their value is questionable but some showed promising results and more studies should be conducted to explore the value of these tests.<sup>(24)</sup>

### The Value of Chest Radiograph

Currently, chest radiography is the most common investigation modality used to diagnose pneumonia. At one end stands the typical appearance of severe lobar consolidation, known to be strongly associated with bacterial pneumonia and at the other end there are the mild interstitial and perihilar changes often associated with viral infections or asthma (Fig. 1). In pediatric practice, it seems acceptable to consider a febrile child as having bacterial pneumonia if the clinical picture is associated with lobar or segmental consolidation on the chest radiograph. The classical chest radiographic presentation of pneumococcal pneumonia is as a lung alveolar infiltration, usually confined to one lobe or a part of it.<sup>(17,25)</sup> This finding is believed to be present in about 85% of all cases. In studies using lung aspirates along with the appropriate radiological findings, the rate of detection of *S. pneumoniae* was high.<sup>(17,26,27)</sup> In most instances where patients with lobar consolidation were studied, the predominant bacterial pathogen was *S. pneumoniae*.<sup>(28)</sup> In addition, a 37% reduction of pneumonia with alveolar infiltrates was demonstrated in children vaccinated with pneumococcal conjugated compared with the unvaccinated children.<sup>(29)</sup> While the contribution of bacterial infections, mainly due to *S. pneumoniae*, in cases with lobar consolidation was demonstrated in lung aspiration studies, their contribution to cases with interstitial non-alveolar cases was not proved.<sup>(16)</sup>

Previous studies suggested considerable variation in interpretation of chest radiographs by clini-

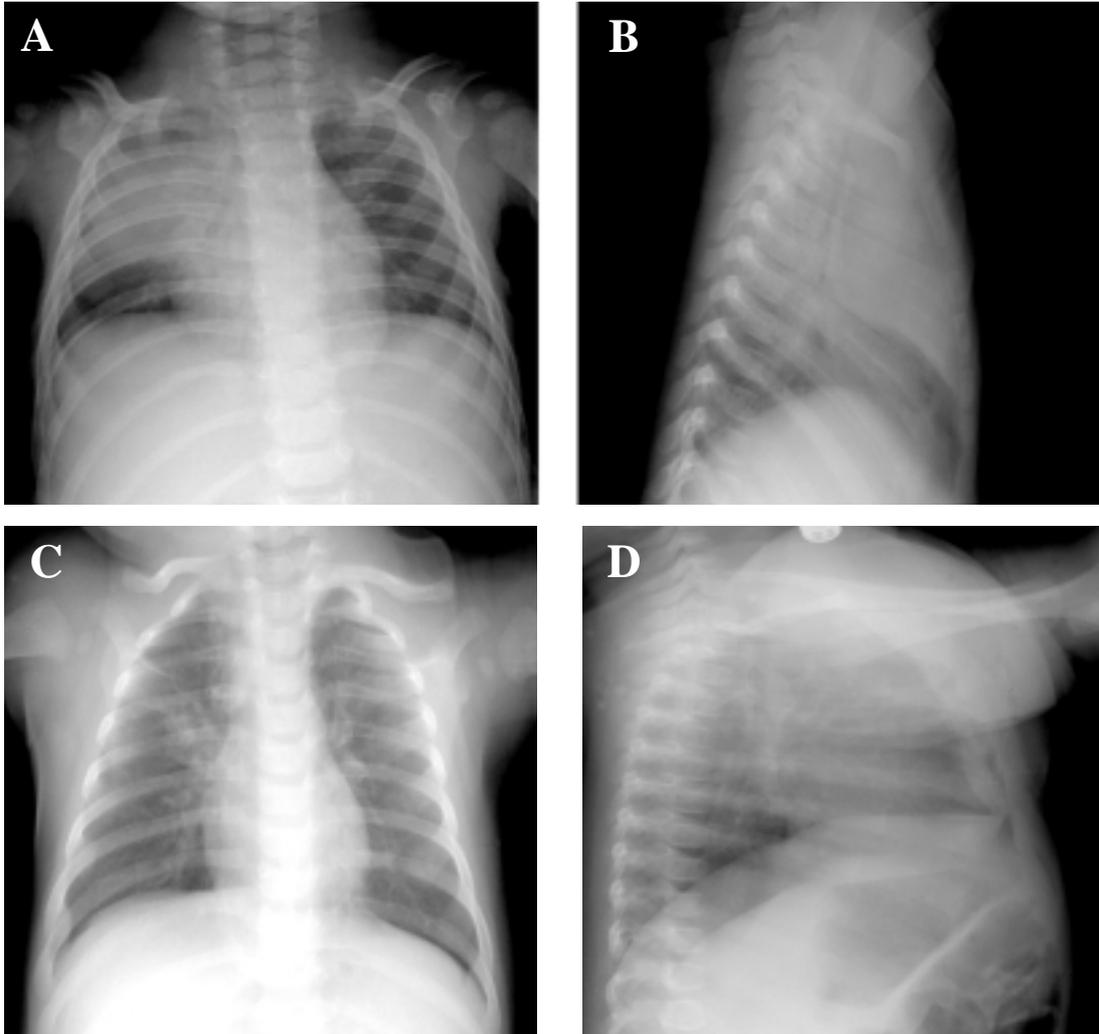
cians and radiologists as well.<sup>(30,31)</sup> Agreement on the presence or absence of consolidation or the presence or absence of infiltrates was high. No standard criteria were used in order to determine a correct chest X-ray diagnosis of pneumonia in previous studies.<sup>(4)</sup> Since pneumonia is an important endpoint for vaccine trials against *S. pneumoniae* and *H. influenzae*, the World Health Organization (WHO) Radiology Group developed in 2001 diagnostic criteria aimed mainly for the epidemiological and vaccine studies measuring pneumonia as an endpoint.<sup>(32)</sup> These criteria were used in several studies evaluated different pneumococcal conjugated vaccines.<sup>(29,33)</sup> In these studies significant efficacy rates were demonstrated for the reduction of alveolar pneumonia (using the WHO definitions).

### Treatment of CAP in Children

Successful treatment of infections caused by bacteria depends on: (1) Risk factors related with the infected host; (2) susceptibility of the organism to the prescribed drug; and (3) dosage of antibiotic drug that can provide sufficient level at the site of infection.<sup>(34)</sup>

Penicillin is the drug of choice for susceptible *S. pneumoniae* strains, defined as those with penicillin MIC < 0.1 µg/ml. Regular doses of penicillin exceed this concentration in blood and most other body fluids. Penicillin G is the most common parenteral drug used in the treatment of pneumococcal infection with doses ranging from 50,000 units/Kg/day for minor infections to 300,000 units/Kg/day for meningitis. Other forms of penicillin such as penicillin V or ampicillin present no advantages over penicillin G in serious infections. In some areas of the world where resistance is uncommon, erythromycin and cephalosporins are alternative treatments for penicillin-allergic patients. Many other agents such as clindamycin, tetracycline, and trimethoprim-sulfamethoxazole, are active against *S. pneumoniae* but resistance to many of these agents is increasing rapidly in many regions of the world.

Standard guidelines developed by WHO recommend that children diagnosed with non-severe pneumonia (without lower chest wall indrawing but with fast breathing) should be treated at home with oral antibiotic. Those diagnosed as severe pneumonia (with lower chest wall indrawing) should be admitted and given parenteral antibiotics such as ben-



**Fig. 1.** Posterior anterior view (A) and lateral view (B) of alveolar pneumonia and posterior anterior view (C) and lateral view (D) of non-alveolar pneumonia.

zylpenicillin or ampicillin. Application of these guidelines in developing countries has resulted in decreased mortality from acute respiratory infection.<sup>(35,36)</sup>

In some areas, treatment of penicillin non-susceptible *S. pneumoniae* (PNSP) has become a challenge and reports of treatment failure, especially in invasive multi-drug resistant (MDR) *S. pneumoniae* infections, have increased.<sup>(37)</sup>

Isolates of *S. pneumoniae* resistant to penicillin are frequently resistant to other drug classes such as cephalosporins, macrolides, quinolones and trimethoprim-sulfamethoxazole.<sup>(38)</sup> The treatment challenge is high because of MDR *S. pneumoniae*,

which may lead to treatment failures. For example, macrolide resistance is much more common in penicillin resistant than in non penicillin resistant *S. pneumoniae* isolates leading to treatment failure such as described in otitis media.<sup>(39)</sup>

In most cases the treatment should be initiated empirically based on clinical and laboratory findings. Antibiotic treatment is generally based on knowledge of the epidemiology and antibiotic susceptibility of the most common organisms causing pneumonia.

Oral  $\beta$ -lactam antibiotic such as amoxicillin, cefuroxime axetil and amoxicillin/clavulanate are all appropriate options as first line therapy of ambulatory community-acquired pneumonia in children < 5

years of age.<sup>(40)</sup> In the majority of cases of pneumonia caused by penicillin-intermediately resistant *S. pneumoniae* the outcome was favorable in children treated by penicillin G 100,000 to 300,000 U/kg per day or 100-300 mg/kg per day divided in 4 to 6 doses as well as amoxicillin 25-50 mg/kg/day in 3 divided doses or amoxicillin-clavulanate and cefuroxime 27-100 mg/kg/day in 3 divided doses.<sup>(9)</sup>

No differences in outcome were found between patients treated for pneumococcal community acquired pneumonia by amoxicillin-clavulanate compared with ceftriaxone.<sup>(41)</sup>

For immunocompetent hospitalized children who are not critically ill, parenteral treatment with  $\beta$ -lactams such as cefuroxime, cefotaxime or ampicillin (with or without  $\beta$ -lactamase inhibitors) in an appropriate option, covering both *S. pneumoniae* and most other potential organisms.<sup>(40)</sup>

Comparison between adult patients with pneumonia caused by penicillin or cephalosporin resistant organisms and patients with pneumonia due to susceptible organisms, both treated by penicillin or cephalosporin, showed no differences in outcome.<sup>(42-44)</sup>

Pleural empyema caused by penicillin-nonsusceptible *S. pneumoniae* appear to be associated with younger age and previous antibiotic treatment. No significant differences were found between patients with empyema caused by susceptible compared with those with non-susceptible *S. pneumoniae* in duration of fever and tachypnea, need of surgical treatment, bacteremia incidence, mean duration of therapy, or length of hospital stay.<sup>(45)</sup>

Treatment failure and breakthrough meningitis was reported in a patient with pneumonia initially treated with cefotaxime and cefuroxime, who was infected by highly resistant *S. pneumoniae* (penicillin MIC 2  $\mu$ g/ml, cefuroxime MIC 8  $\mu$ g/ml, cefotaxime MIC > 2  $\mu$ g/ml).<sup>(46)</sup> Thus, in critically ill patients with highly resistant *S. pneumoniae* some authorities recommend, in addition to third generation cephalosporins, the use of vancomycin or in older patients fluoroquinolones that are active against *S. pneumoniae*.<sup>(40)</sup>

In  $\beta$ -lactams allergic patients, erythromycin and other macrolides are favored.<sup>(47,48)</sup> In some areas, macrolide resistance is common and may lead to treatment failure.<sup>(49,50)</sup> Breakthrough cases with pneumococcal bacteremia while treated with clar-

ithromycin or azithromycin for community acquired pneumonia were reported.<sup>(50)</sup>

In cases of pleural fluid or empyema in patients infected by highly resistant organisms, vancomycin or rifampin may be added if no clinical response is achieved within 48 to 72 hours.<sup>(51)</sup>

Drugs that are not appropriate for treating critically ill patients with pneumococcal pneumonia are the first generation cephalosporins, ceftazidime and ticarcillin, since the majority of penicillin-resistant *S. pneumoniae* are resistant to these drugs.<sup>(52,53)</sup>

Trimethoprim-sulfamethoxazole is not recommended for the treatment of *S. pneumoniae* pneumonia due to high prevalence of resistance.<sup>(40)</sup>

Duration of treatment is related to the clinical presentation, clinical response to treatment and underlying diseases of the patient and it is generally 7-14 days. For hospitalized patients 5-7 days of parenteral treatment followed by 7 days of oral therapy is recommended,<sup>(48,51)</sup> but many clinicians use a shorter treatment of 7-10 days in total.

### Influences on Quality of Life

Childhood community-acquired infections have an important impact on society and are a frequent cause of physician visits, antibiotic and over-the-counter drugs consumption, work loss and reduction of quality of life.<sup>(54)</sup> The direct cost of an episode of pneumonia may be measured by physician visits, cost of chest radiographs and consumption of antibiotics and over-the-counter drugs. The indirect costs such as missing work to care for a sick child, hiring a babysitter and transportation costs are more difficult to assess. Beyond financial considerations, an episode of pneumonia have an impact on the quality of life of patients and their families, including the daily family organization, social activities, stress and parental anxiety.<sup>(54)</sup> This information should be appropriately taken into consideration when deciding on the appropriate antibiotic treatment for this common pediatric condition.

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