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Practice Recommendation

Practice Recommendations for Management of Community Acquired Pneumonia in Children

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On behalf of the CAP Guideline Development Group

Abstract Community acquired pneumonia (CAP) is a common condition encountered in both ambulatory and hospital settings in Hong Kong. Two sets of evidence based international guidelines on management of CAP, the Infectious Diseases Society of America and the British Thoracic Society guidelines, are available, but the local epidemiology, the public health infrastructure, vaccination program, social and economic background are all different from Hong Kong. Therefore not all of the recommendations are relevant to Hong Kong practice. The 2015 Hong Kong paediatric CAP guidance drafted by the CAP guideline development group aims at developing a set of local guidance with reference to international recommendations (including American and British guideline), based on the current available local data (including *Streptococcus pneumoniae* and Macrolide-resistant *Mycoplasma pneumoniae*) and consensus of the panel. Immunocompetent paediatric patients of age range beyond 3 months are the main focused population of the current set of guidance, in both in-patient and out-patient setting.

Key words Community acquired; *Mycoplasma pneumoniae*; Paediatric; Pneumonia; *Streptococcus pneumoniae*

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Introduction

Community acquired pneumonia (CAP) is a common condition encountered in both ambulatory and hospital settings in Hong Kong. From 2000-2005, hospital discharge diagnoses revealed that admission rate for clinical pneumonia was 932 per 100,000 population aged 0-5 years in Hong Kong.[1] This was similar to the rate of 776 per 100,000 population following chart review of systematically recruited children younger than 5 years.[2] CAP has a very wide spectrum of clinical manifestation and severity. An expert panel (CAP guideline development group) has been formed to compile a set of clinical statements and practices to guide and assist clinicians in managing CAP in Hong Kong. The panel consists of paediatricians with special interest in pulmonology and intensive care, paediatric infectious diseases specialists, clinical microbiologists, general paediatrician, emergency

physician, private paediatrician and family physician. This practice parameter is jointly developed by Hong Kong College of Paediatricians, Hospital Authority Central Coordinating Committee (COC) in Paediatrics, Family Medicine, and representative from COC (A&E).

Two sets of evidence based international guidelines on management of CAP, the Infectious Diseases Society of America (IDSA)[3] and the British Thoracic Society (BTS)[4] guidelines, are available, but the local epidemiology, the public health infrastructure, vaccination program, social and economic background are all different from Hong Kong. Therefore not all of the recommendations are relevant to Hong Kong practice. Moreover, specific clinical problems seen in Hong Kong are not addressed in the two sets of international guidelines.

The CAP guideline development group aims at developing a set of local guidance with reference to international recommendations, based on the currently available local data and consensus of the panel. Immunocompetent paediatric patients of age range beyond 3 months are the main focused population of the current set of guidance, in both in-patient and out-patient settings. The management of pneumonia in patients less than 3 months; patients with pre-existing respiratory conditions; hospital acquired pneumonia and pneumonia in immunocompromised patients shall not be included in this set of guidance. The major goal of the panel is to adopt international recommendations relevant for local use. Therefore no further elaboration shall be included for statements or recommendations without any controversy.

The major scope of the current set of guidance includes:

1. To provide update information on local epidemiology of CAP based on the best available published information in Hong Kong.
2. To assist clinicians in not missing a case of clinical pneumonia, at the same time, avoiding over-diagnosing pneumonia resulting in overuse of antibiotics.
3. To fill the gap in international recommendation and provide guidance on management of clinical conditions which are unique in Hong Kong.
4. To promote the effective and appropriate utilisation of laboratory diagnostic tools and antimicrobial agents.

This set of guidance is developed for paediatricians, family physicians working in the private and public sectors, clinicians working in the accident and emergency departments.

The guidance includes the following section:

1. Local epidemiology
2. Clinical features
3. Initial assessment
4. General investigations
5. Microbiology and laboratory diagnosis
6. Chest X-ray (CXR) and complications
7. General management
8. Antibiotics treatment
9. Specific problems: macrolide-resistant *Mycoplasma pneumoniae*
10. Discharge criteria

1. Local Epidemiology

The ever changing epidemiology of CAP is a result of healthcare intervention (such as pneumococcal vaccine), local factors (such as overuse of antibiotics resulting in spread of antimicrobial resistant organisms) and external factors (such as influx of cross-border students and introduction of pathogens which are not endemic in Hong Kong). Combination of factors has resulted in a rapid change in epidemiology of CAP in Hong Kong and there is a need to provide an update and a set of guidance to the local practitioners.

- Establishing exact aetiological diagnosis of pneumonia in children is difficult and often impossible. Studies from overseas indicate that *Streptococcus pneumoniae* is the most frequent bacterial cause of CAP, with or without co-infection with respiratory viruses, despite routine use of pneumococcal conjugate vaccination.[3,4]
- Different breakpoints are currently adopted for interpretation of penicillin and cephalosporin susceptibility of pneumococcal isolates causing meningitis and non-meningitis infections (Table 1). In Hong Kong, low level penicillin resistance is widespread among the pneumococcal isolates from both healthy and sick children with >60% isolates having penicillin minimal inhibitory concentration (MIC) ≥0.12 μg/ml (Figure 1).[5,6]
- Local surveillance by Centre for Health Protection revealed that serotype 3 is the most prevalent type, followed by 19A among pneumococcal isolates from blood and other sterile body fluids of children with invasive pneumococcal disease in 2014.
- Almost all of the serotypes 3 and 19A isolates were

Table 1 Definitions of penicillin and cephalosporins susceptibility for *Streptococcus pneumoniae*

Antimicrobial agent	MIC (μg/ml)[a]		
	Susceptible	Intermediate	Resistant
Penicillin (oral penicillin V)	≤0.06	0.12-1	≥2
Penicillin parenteral (non-meningitis)	≤2	4	≥8
Penicillin parenteral (meningitis)	≤0.06	–	≥0.12
Amoxicillin (non-meningitis)	≤2	4	≥8
Amoxicillin-clavulanate (non-meningitis)[b]	≤2	4	≥8
Ceftriaxone or cefotaxime (non-meningitis)	≤1	2	≥4
Ceftriaxone or cefotaxime (meningitis)	≤0.5	1	2

MIC, minimal inhibitory concentration.

[a]According to the Clinical Laboratory Standards Institute[134]

[b]Breakpoints for the amoxicillin component.

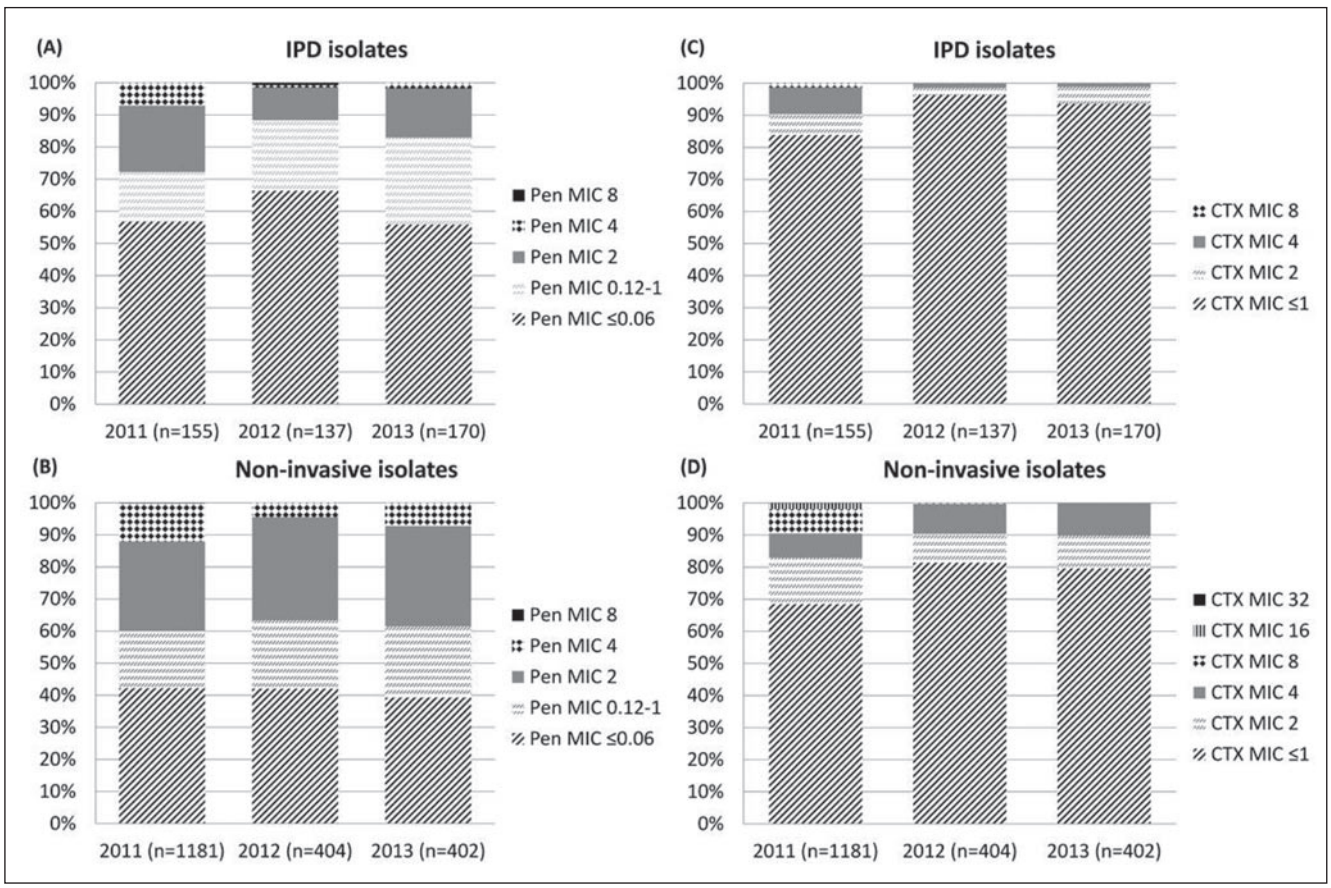

Figure 1 Susceptibility of 462 invasive and 1987 non-invasive pneumococcal isolates to penicillin and cefotaxime, 2011-2013, Hong Kong. This was obtained from the Public Health Laboratory Service Branch sentinel data from the major public and private laboratories. IPD, invasive pneumococcal disease; Pen, penicillin; CTX, cefotaxime.

macrolide-resistant. In the past 3 years, small numbers of severe and even fatal pneumococcal pneumonia caused by serotype 3 were observed. In several children, the disease was complicated by rapid onset of empyema and haemolytic-uraemic syndrome. While serotype 3 is included in the 13-valent pneumococcal conjugate vaccine, there is no clinical evidence that it protects against infection by this serotype. This serotype was removed from the 11-valent precursor of PCV10 after an otitis media trial did not show serotype-specific efficacy[7] In the United Kingdom, no effectiveness of PCV13 was shown for serotype 3.[8] Furthermore, the correlate of protection cutoff for serum IgG concentration for this serotype was determined to be 2.83 μg/ml which is substantially higher than the previously presumed value of 0.35 μg/ml.[8] The required antibody concentration is rarely reached from vaccination.

- Please see section 9 for the epidemiology of macrolide-resistant *Mycoplasma pneumoniae* (MRMP) infections
- Less frequent causes include non-encapsulated (non-typeable) *Haemophilus influenzae* and *Moraxella catarrhalis*[3,4,9,10]
- Group A streptococcus and *Staphylococcus aureus* are less common causes of pneumonia but can be associated with serious diseases and complications. In our locality, macrolide resistance is highly prevalent among both Group A streptococcus (50-80%) and *S. aureus* (30%) isolates from children, both inpatients and outpatients.[11,12]
- Group A streptococcus, *S. pneumoniae* and *S. aureus* may cause secondary bacterial pneumonia following influenza. *S. pneumoniae* following influenza is an important cause of pneumonia deaths.
- Table 2 summarised the prevalence of antimicrobial resistance of common respiratory pathogens in Hong Kong.

2. Clinical Features of CAP

It is recognised that there is considerable overlap in the clinical features of various respiratory infections syndromes.[13] Although it is important for the clinician to make distinction between upper respiratory infection, bronchitis and pneumonia, it is known that often other parts of the respiratory tract, being a continuum, are affected at the same time. The clinical distinction of these syndromes therefore serves as an indication of the part of the respiratory tract most affected, as indicated by the symptoms and signs of the patient. However, the diagnosis of these clinical syndromes will help the clinician to consider the main possible causes of the infection, to assess its severity and to institute treatment.

The diagnosis of various respiratory infection syndromes are therefore mainly clinical, sometimes assisted by an X-ray of the chest or ultrasound imaging. Six main syndromes have been identified:

a. Upper respiratory infection (rhinitis, pharyngitis, laryngitis, tonsillitis). This is characterised by the presence of nasal symptoms including runny or blocked nose, sore throat and/or hoarseness in the older child, and cough, with examination findings confirming congestion and inflammation in the corresponding parts, coupled often with fever and/or general malaise and cervical lympadenopathy. An upper respiratory infection is often caused by a virus, although in some occasions, this is due to *Streptococcus pyogenes* or Staphylococcus.
b. Bronchitis. In addition to the symptoms presented above, cough, dry or phlegmy, is a prominent feature, but without clinical features of pneumonia. Fever and/or general malaise and cervical lymphadenopathy are often present. Research has suggested that the majority are due to viruses.[14]
c. Croup. In addition to the symptoms of respiratory infection, there is feature of upper thoracic airway obstruction, namely, stridor, hoarseness and a barking cough. Depending on whether the obstruction is extra- or intra-thoracic, the stridor may vary from inspiratory to both inspiratory and expiratory. The lower the obstruction, the more such sound will resemble a wheeze.
d. Bronchiolitis. Symptoms of respiratory infection in an infant are coupled with symptoms and signs of small airway obstruction, namely, wheezing, prolonged

Table 2 Prevalence of macrolide resistance among common bacterial pathogens associated with pneumonia, 2011-2014, Hong Kong

	% macrolide-resistant[a]		
Streptococcus pneumoniae	***Mycoplasma pneumoniae***	***Staphylococcus aureus***	**Group A streptococcus**
70%	30-70%	30%	50-80%

According to data from the Public Health Laboratory Service Branch, Centre for Health Protection, public and private microbiology laboratories and publications by local investigators.[5,11,12,97,99,102,135]

[a]Including erythromycin, clarithromycin, roxithromycin and azithromycin

expiration, crackles, and chest hyperinflation. Bronchiolitis is predominantly caused by viruses.

e. Pneumonia. When cough being a prominent feature, coupled with the presence of clinical signs of consolidation, collapse or effusion, pneumonia is highly likely, especially when coupled with corresponding X-ray findings. World Health Organization (WHO) recommends that tachypnea or dyspnoea are essential for diagnosing pneumonia.[15] This is a very specific and reliable diagnostic feature in developing countries. However, in developed countries, pneumonia is also found with little signs of respiratory distress.

f. Otitis media and sinusitis. They can rightly be considered respiratory infections, with its diagnosis made by demonstrating inflammation in the corresponding sites.

- Children with CAP may present with fever, tachypnoea, breathlessness or difficulty in breathing, cough, wheeze or chest pain. These clinical features vary with the age of the child and tend not to be very specific for diagnosis of CAP.
- Bacterial pneumonia should be considered in children when there is persistent or repetitive fever >38.5°C together with chest recession and a raised respiratory rate.

3. Initial Assessment (Severity Assessment)

Outpatient Setting

Indication for referral and admission to hospital:

- Oxygen saturations <94% or cyanosis[16]
- Auscultation revealing absent breath sounds with a dull percussion note should raise the possibility of a pneumonia complicated by effusion[16,17]
- Respiratory rate >60 breaths/min in <2 months; >50/min in 2-11 months; >40/min in 1-5 years (WHO definition)[18,19]
- Significant tachycardia for level of fever (values to define tachycardia vary with age and with temperature);[20]
- Prolonged central capillary refill time >2 seconds[16]
- Difficulty in breathing
- Intermittent apnoea, grunting
- Poor feeding
- Chronic conditions (e.g. congenital heart disease, chronic lung disease of prematurity, chronic respiratory conditions leading to infection such as cystic fibrosis, bronchiectasis, immune deficiency). Further management of CAP in this group of patients is out of the scope of this guidance and will not be discussed here.
- Young infants with suspected bacterial CAP
- Children and infants for whom there is concern about careful observation at home or who are unable to comply with therapy or unable to be followed up

Inpatient

- A child in hospital should be reassessed medically if condition deteriorates after admission with increased work of breathing or if the child is becoming distressed or agitated.
- Children on adequate therapy should demonstrate clinical and laboratory signs of improvement within 48-72 hours. For children whose condition deteriorates after initiation of antimicrobial therapy or who show no improvement within 48-72 hours, further assessment and investigations (e.g. acute phase reactants, additional radiological examination and reassessment for possible co-infection, antimicrobial resistance or unusual pathogens) should be performed.[21-31] Please refer to section 5 for further details.
- Medical reassessment should always look for signs of overwhelming infection and septicaemia and dehydration.[32,33]
- Auscultation revealing absent breath sounds with a dull percussion note should raise the possibility of a pneumonia complicated by effusion or empyema thoracis.[16,17,34-37]
- Other issues need to consider include whether appropriate drug treatment is given at an adequate dosage and frequency, and by an appropriate route, coexistent diseases such as underlying airway obstruction, cystic fibrosis, immune deficiency or complications of CAP including necrotising pneumonia[38-40] and haemolytic-uraemic syndrome.[41] The management of CAP in special group of patients is out of the scope of this guidance.

4. General Investigations

Inpatient

- Markers of inflammation, such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) concentration, or serum procalcitonin concentration, cannot be used as the sole determinant to distinguish between viral and bacterial causes of CAP.[42-54] C-reactive protein is not useful in the management of uncomplicated pneumonia and should not be measured routinely.

- For more serious disease, complete blood counts and acute-phase reactants may provide useful information for clinical management and may be useful in conjunction with clinical findings to assess response to therapy.[41,55-58]
- Pulse oximetry should be performed in all with pneumonia and suspected hypoxaemia.
- Patients whose oxygen saturation is 92% while breathing air should be treated with oxygen given by nasal cannulae, high flow delivery device, head box or face mask to maintain oxygen saturation >92%.[59]
- The presence of hypoxaemia should guide decisions regarding site of care and further diagnostic testing.

5. Microbiological Investigations of Community-acquired Pneumonia in Children

- Microbiological investigations should not be considered routinely in those with mild disease or those treated in the community.
- Microbiological diagnosis should be attempted in children with moderate to severe pneumonia or those with complications of CAP.
- Blood cultures should not be routinely performed in non-toxic children with CAP managed in the outpatient setting.
- Blood cultures should be obtained in children requiring hospitalisation for presumed bacterial CAP that is moderate to severe, particularly those with complicated pneumonia.
- Blood cultures should be repeated in children who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration after initiation of antibiotic therapy.
- Repeated blood cultures in children with clear clinical improvement are not necessary to document resolution.
- Sputum samples for culture and Gram smear should be obtained in hospitalised children who can produce sputum, in those who require paediatric intensive care admission, and in those with complications of CAP.
- Nasopharyngeal secretions for diagnosis of influenza virus and other common respiratory viruses by rapid tests (e.g. antigen assay or polymerase chain reaction) should be used in the evaluation of children with moderate or severe CAP. In the absence of clinical or radiographic findings that suggest bacterial coinfection, a positive influenza test may decrease both the need for additional diagnostic studies and antibiotic use, while guiding appropriate use of antiviral agents.
- When clinical, laboratory or radiographic findings are suggestive of a bacterial infection, a positive rapid test for respiratory viruses supports the presence of coinfection, which may be associated with more severe disease and necessitates closer monitoring and more intensive therapy.
- Testing for respiratory viruses other than influenza virus can modify clinical decision making in children with suspected pneumonia because antibacterial therapy will not routinely be required for these children in the absence of clinical, laboratory, or radiographic findings that suggest bacterial co-infection.
- Viral cultures of nasopharyngeal secretions or sputum are not of any utility in making clinical management decisions.
- The clinician should obtain tracheal aspirates at the time of initial endotracheal tube placement in children requiring mechanical ventilation for Gram stain and culture, as well as clinically and epidemiologically guided rapid molecular testing for viral pathogens, including novel or emerging viruses such as avian influenza virus and Middle East respiratory syndrome coronavirus.
- Bronchoscopic or blind protected specimen brush sampling, bronchoalveolar lavage, percutaneous lung aspiration, or open lung biopsy should be reserved for both immunocompetent and immunocompromised children with severe CAP if initial diagnostic tests are negative.
- Serology for respiratory viruses is not of any utility in making clinical decision because specific antibodies may take 2 weeks or more to develop.
- *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* (previously *Chlamydia pneumoniae*) serology are not of any utility in making clinical decisions because of poor sensitivity and specificity. For the details of laboratory diagnosis of *M. pneumoiae* and testing of macrolide resistance, please refer to section 9 below.
- If obtained, pleural fluid should be sent for Gram smear, culture, pneumococcal antigen detection, and PCR for pneumococcus or other suspected atypical respiratory pathogens.
- Urinary antigen detection tests are not recommended for the diagnosis of pneumococcal pneumonia in children. False-positive tests are common in children who are colonised with pneumococcus or have recently received pneumococcal vaccines.

- Urinary antigen detection may be helpful as negative predictor of pneumococcal infection in older children.

Attempting an aetiologic diagnosis of CAP in children is challenging. An accurate and rapid diagnosis of the pathogen can inform clinical decision making, resulting in improved care with targeted narrow-spectrum antimicrobial therapy, fewer unnecessary tests and procedures, and potentially shortened hospitalisation.[3,60-63] There is, unfortunately, no single diagnostic test apart from examining a direct lung aspirate that can be considered the gold standard.[64] Determining the aetiology of CAP is critically dependent on the thoroughness of the search and the tests used. The more tests that are performed, the more potential causes may be identified. In a review of European paediatric studies, the microbial cause of pneumonia could be identified in 20 to 60% of cases depending on the extent of laboratory testing performed.[65] In a UK study, a pathogen was isolated in up to 60% of cases, and considered a definite or probable cause of CAP in 51% of children.[66]

Despite the limitations of available laboratory tests, establishing a microbiologic diagnosis is important in children with severe or complicated CAP, in those with unusual but treatable causes, and in those infected by novel or emerging pathogens.[67] Even when a respiratory pathogen has been identified in upper respiratory tract secretions, its causal role in pneumonia can be difficult to assess as this does not necessarily imply that it is the aetiologic agent of the patient's lower respiratory disease. Likewise, the identification of a potentially causative pathogen does not preclude the possibility of an aetiologic contribution from other pathogens. Respiratory viral infections are frequently complicated by bacterial superinfections and viral-bacterial coinfections are not uncommon.[65,68] Viral and bacterial coinfections were identified in 23% of children with pneumonia evaluated at a tertiary-care children's hospital.[69]

Sputum samples for culture and Gram smear should be obtained in hospitalised children who can expectorate sputum, in those who require intensive care, and in those with complications of CAP. However, infants and young children are often unable to produce sufficient sputum for collection and cultures of these specimens may be contaminated by bacterial flora in upper respiratory secretions which do not correlate with those infecting the lower respiratory tract.

Despite the low overall yield, blood cultures are essential for the investigation of children hospitalised for CAP and in children who fail to demonstrate clinical improvement or have progressive clinical deterioration after initiation of antibiotic therapy. However, blood cultures cannot detect atypical bacterial pathogens such as *M. pneumonia*e and *C. pneumoniae,* and all viral pathogens. Repeated blood culture to confirm sterilisation with appropriate antimicrobial therapy is not necessary in children who clearly demonstrate clinical improvement. The overall impact of blood cultures on clinical management may be small because of the low prevalence of accompanying bacteraemia. The cost-effectiveness of obtaining blood cultures in all children hospitalised for CAP is unknown.

A viral aetiology of CAP may be inferred by evaluation of nasopharyngeal secretions with rapid tests (e.g. antigen assay or PCR) for influenza and other common respiratory viruses. Identification of a respiratory virus may obviate the need for antibiotic therapy in the absence of findings suggestive of bacterial coinfection while detection of influenza virus can guide appropriate antiviral treatment.[62,70,71] Viral cultures of respiratory secretions are not useful for therapeutic decision making as results will only be available after some time.

For diagnostic evaluation of parapneumonic effusion or empyema, pleural fluid, if obtained, should be sent for Gram smear, culture, pneumococcal antigen detection, and PCR for pneumococcus or other suspected atypical respiratory pathogens. In Hong Kong, an apparent increase in the incidence of pneumococcal pleural empyema caused by serotype 3 is observed. It should be noted that serotype 3 pneumococcal empyema is often culture negative but presence of the pathogen in the pleural pus could be readily detected by pneumococcal specific PCR tests. Urinary antigen detection tests are not recommended for the diagnosis of pneumococcal pneumonia in children as false-positive results are common. Positive results of pneumococcal urinary antigen tests do not reliably distinguish children with pneumococcal pneumonia from those who are merely colonised with pneumococcus in their nasopharynx.[72-75] False-positive results may also occur in those who have recently received pneumococcal vaccines. However, urinary antigen detection may be helpful as negative predictor of pneumococcal infection in older children.

6. Chest Radiography

Outpatient

- If patient is stable and can be managed in outpatient setting, routine chest radiographs are usually not necessary to confirm the diagnosis of CAP.

- If patient fails to respond to initial antibiotic therapy, or have significant respiratory distress, or hypoxaemia, or suspected to have complications such as parapneumonic effusions, chest radiographs should be obtained.

Inpatient

- For patient hospitalised for management of CAP, chest radiographs are recommended to document and assess the extent of pneumonia, and to identify any associated complications.

Follow-up Chest Radiography

- In a child recovering uneventfully from an episode of uncomplicated CAP, repeated follow up CXR is not routinely required.[76-80]
- Repeated chest radiographs 4-6 weeks after the diagnosis of CAP should be obtained in patients with recurrent pneumonia involving the same lobe and in patients with lobar collapse at initial chest radiography with suspicion of an anatomic anomaly, chest mass, or foreign body aspiration.
- If patients fail to show improvement, or have progressive deterioration within 48-72 hours after initiation of antibiotics, repeated chest radiographs should be obtained.

7. General Management

Community

Advise parents and carers about:

- Management of fever
  - use of antipyretics
- Preventing dehydration
- Identifying signs of deterioration
- Identifying signs of other serious illness
- How to access further healthcare (providing a 'safety net'):
  - provide the parent or carer with information on warning symptoms and how further healthcare can be accessed;
  - arrange a follow-up appointment at a certain time and place;
  - liaise with other healthcare professionals to ensure the parent/carer has direct access to further assessment for their child.

Inpatient

- Nasogastric tubes may compromise breathing and should be avoided in severely ill children and especially in infants with small nasal passages. If use cannot be avoided, the smallest tube should be passed down the smaller nostril.[81, 82]
- Plasma sodium, potassium, urea and/or creatinine should be measured at baseline and monitor as appropriate when on intravenous fluids.
- Chest physiotherapy is not beneficial and should not be performed in children with pneumonia.[83-86]

Indications for Intensive Care Admission

- A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child has impending respiratory failure, or sustained tachycardia, inadequate blood pressure, or need for pharmacologic support of blood pressure or perfusion.
- A child should be admitted to an Intensive Care Unit (ICU) if the pulse oximetry measurement is <92% on inspired oxygen of >0.50 or if the child has altered mental status, whether due to hypercarbia or hypoxaemia as a result of pneumonia.[87]
- Other features that suggest a child requires transfer include: clinical evidence of severe respiratory distress and exhaustion, with or without a raised arterial carbon dioxide tension; recurrent apnoea or slow irregular breathing.[88]
- A child should be admitted to an ICU if the child requires invasive ventilation (e.g. endotracheal tube),[69] or noninvasive positive pressure ventilation (e.g., continuous positive airway pressure or bi-level positive airway pressure).
- Severity of illness scores should not be used as the sole criteria for ICU admission but should be used in the context of other clinical, laboratory, and radiologic findings.

Complications

- If patients are not responding well to treatment, evaluation should be considered to exclude complications
- Common possible complications include:
  - Pyogenic complications: empyema, lung abscess and necrotising pneumonia, bacteraemia with secondary metastatic foci.
  - Non-pyogenic complications: Pneumococcal-associated haemolytic uremic syndrome, autoimmune phenomenon and concomitant extrapulmonary manifestations in mycoplasma (e.g. encephalitis in *M. pneumoniae*-associated CAP).

8. Antibiotics

Empirical Antibiotics Treatment

- Empirical antibiotics regimen for CAP in children should include antibiotics which are able to cover *S. pneumoniae*.
- Macrolides (such as erythromycin, clarithromycin, azithromycin, roxithromycin) should not be used as sole empirical treatment of CAP
- At the current level of pneumococcal penicillin resistance, oral cephalosporins (cephalexin, cefaclor, cefuroxime axetil, ceftibuten) would not provide reliable coverage for many pneumococci.[89]
- In Hong Kong, 30-40% and approximately 10% of the isolates from children <5 years had penicillin MIC of 2 μg/ml and 4 μg/ml, respectively in 2011-2013 (Figure 1 and Table 1).
- To achieve the appropriate drug exposure in lung infected by relatively resistant pneumococci, a higher total daily dose of oral amoxicillin is required. If amoxicillin-clavulanate is used, dosage should be calculated by using the amoxicillin component. Given that an increased amount of clavulanate is associated with higher incidence of diarrhoea in a dose-dependent manner, preparation that could provide the required amoxicillin dose with the least amount of clavulanate would be preferred (Table 3).
- In predicting efficacy of dosing regimen, pharmacokinetic-pharmacodynamic modeling and Monte Carlo simulations are often used to predict the probability of a successful outcome by using information about the antibiotic dose, serum concentration, and the MIC of the organism and taking into consideration biological variations (e.g. inter-subject variations). Fonseca et al evaluated amoxicillin pharmacokinetics in infants/children (aged 5-52 months) with pneumonia receiving oral amoxicillin. These investigators found highly variable amoxicillin levels with 5- to 30-fold variances.[90] Large inter-subject variations in amoxicillin levels in middle ear fluids have also been found after oral administration of the same amoxicillin dose.[91] Similarly, variability in amoxicillin pharmacokinetics following oral administration was reported for studies involving adults.[92]
- To achieve the appropriate exposure in lung infected by pneumococci with penicillin MIC of 2 μg/ml, amoxicillin at a total daily dose of 90 mg/kg/day (given 3 times daily) is predicted to achieve a clinical and microbiological cure in 90% of children.[3,93] The probability of therapeutic target attainment (40% fT>MIC, i.e. plasma concentration remains above the minimum inhibitory concentration for at least 40% of the dosing interval) for penicillin MIC 2 μg/ml following 45 mg/kg/day is less than 60%.[3, 90]
- In children without risk factor for penicillin resistance, initial amoxicillin dosing of 45 mg/kg/day in three divided doses may be used. In children at risk of penicillin-resistant pneumococci, an even higher daily dose of amoxicillin (90 mg/kg/day in 2 to 3 divided doses) is required. Children who have taken antibiotics in the recent 3 months are considered to be at risk for penicillin resistance.[94]
- Parenteral anti-pneumococcal 3rd generation cephalosporins (P3GC) such as ceftriaxone and cefotaxime are effective alternatives for treatment of

Table 3 Amount of amoxicillin and clavulanate in different local preparations of this drug combination

Trade name of product (manufacturer)	Availability by amount of amoxicillin/clavulanate per 5 ml suspension				
	125 mg/31.25 mg	200 mg/28.5 mg	250 mg/62.5 mg	400 mg/57 mg	600 mg/42.9 mg
Amoksiklav (Sandoz)	Yes	–	–	–	–
Augmentin (GSK)	Yes	–	–	Yes	–
Clamovid (Hovid)	Yes	–	–	Yes	–
Curam (Sandoz)	Yes	–	Yes	Yes	–
Fleming (Medrelch)	Yes	Yes	Yes	Yes	–
Moxiclav (Medochemie)	Yes	–	Yes	–	–
Quali-mentin (Quality Pharm)	Yes	–	–	–	–
Amount of amoxicillin per kg per day given if 5 ml BD of the suspension is given to a 20 kg child	12.5 mg/kg/day	20 mg/kg/day	25 mg/kg/day	40 mg/kg/day	60 mg/kg/day
Daily amount of clavulanate if 5 ml BD	62.5 mg	57 mg	125 mg	94 mg	85.8 mg

According to MIMS Hong Kong online (Last accessed 20 May 2015)

S. pneumoniae, including the great majority of penicillin-non-susceptible strains. In the absence of positive culture and sensitivity results, children with presumed pneumococcal pneumonia may be treated with an entire course of P3GC (if failed oral amoxicillin-clavulanate) or be stepped down to high dose amoxicillin-clavulanate (90 mg/kg/day of the amoxicillin component in 2 to 3 divided doses).

- For CAP patients with true penicillin allergy, the choice of antibiotics depends on the suspected aetiology. If pneumococcus is the suspect, and if these are patients with severe disease treated as in-patients, the options are clindamycin or vancomycin. For patients with mild diseases treated as out-patients, the options are clindamycin or quinolones. However, most patients who think they have "penicillin allergy" actually do not have penicillin allergy.

Known Pathogen Therapy for *S. pneumoniae*

- Laboratory should report MIC of penicillin (and other beta-lactams, if available) and specify whether interpretation is based on oral penicillin, intravenous penicillin (nonmeningitis), or intravenous penicillin (meningitis) breakpoint to avoid misunderstanding by clinicians.
- Penicillin (parenteral), ampicillin (parenteral) or amoxicillin (oral or parenteral) are the beta-lactam drugs of choice for the great majority of pneumococcal strains.
- After culture result becomes available, choice and dose of antibiotic should be adjusted according to sensitivity result. For isolate with penicillin MIC ≤1 μg/ml, high dose amoxicillin-clavulanate may be stepdown to 45 mg/kg/day (amoxicillin component) in three divided doses.

Since *S. pneumoniae* is the most common cause of CAP, the empirical antimicrobial treatment in both outpatient and inpatient setting should be able to cover *S. pneumoniae*. More than 70% of the local *S. pneumoniae* isolates are resistant to macrolide, and almost all isolates are resistant to oral cephalosporins (cephalexin, cefaclor, cefuroxime axetil, ceftibuten).[89] Utilisation of these agents would result in treatment failures.

According to the Public Health Laboratory Service (PHLS) sentinel data from all public and private laboratories in 2011-2013 (Figure 1),[89] almost 90% of the *S. pneumoniae* isolates had a penicillin MIC ≤2 μg/ml. *S. pneumoniae* with penicillin MIC =4 μg/ml (intermediate susceptibility to penicillin) is very rare and no isolates had a penicillin MIC is ≥8 μg/ml. The panel therefore recommends amoxicillin equivalent 45 mg/kg/day for mild CAP in children with no prior treatment of beta-lactams, and escalation to 90 mg/kg/day or switch to parenteral P3GC if no clinical improvement after 48 hours. For moderate to severe CAP irrespective of prior treatment, amoxicillin equivalent 90 mg/kg/day right from start. Vancomycin is not indicated for empirical treatment of CAP unless there is concomitant evidence of meningitis, severe adverse reaction towards beta-lactam antibiotics (such as cytopenia, Steven-Johnson syndrome, toxic epidermal necrolysis and type I anaphylatic reaction) or the child presents with septic shock and there is no way to exclude meningitis infection.

Duration of Antibiotic Treatment

- As few studies have investigated duration of antibiotic treatments, clinical judgment is required in determining the duration of antibiotic treatment. The factors that need to be considered include patient's clinical response, severity of the infection, *in-vitro* susceptibility of the pathogen, presence of complications and side effects.
- In cases initially treated with intravenous antibiotics, a switch to oral therapy should be considered as soon as the child's clinical condition has improved and oral drugs are well-tolerated.[3,95]
- In clinical trials, the total course of antibiotic treatment is often 7 to 10 days, although shorter courses may be just as effective for milder disease managed on an outpatient basis.[3,4,95]
- Longer treatment courses (>10 days) may be required for CAP complicated by parapneumonic effusion, empyema, or lung abscess but data from clinical trials are lacking. If drainage is adequate, treatment for 2 to 4 weeks is adequate for most children.
- Infection caused by certain pathogens, notably community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA) may also require longer treatment than those caused by *S. pneumoniae*. Vancomycin and linezolid are active against almost all CA-MRSA isolates.

9. Specific Problem: Management of Macrolide-resistant *M. pneumoniae*

Epidemiology

- *M. pneumoniae* is another major cause of CAP in children and young adults. Up to 40% of CAP in children >5 years of age has been attributed to *M. pneumoniae*.[96]

- *M. pneumoniae* has always been considered a disease of school aged children,[3] but a recent study has demonstrated a high rate of *M. pneumoniae*-associated CAP in younger children, where 18% were infant age group 0-1 years and 30% were between 2-11 years.[97]
- Both local and overseas data showed that respiratory tract infections due to *M. pneumoniae* may increase several times during epidemics that occur every 4 to 7 years.[9,10,98]
- In Hong Kong, a study involving 208 children hospitalised in the New Territories West cluster in 2010-2013 found that 70.8% of *M. pneumoniae* were macrolide-resistant.[97,99] Another study involving 1433 children hospitalised in the Hong Kong West cluster reported that prevalence of macrolide-resistant *M. pneumoniae* (MRMP) had significantly increased from 13.6% in 2011 to 30.7% in 2012, 36.6% in 2013 and 47.1% in 2014.[98] MRMP infections have been associated with persistence of symptoms (fever and cough), slower reduction in bacterial load, longer length of hospitalisation, higher chance of requiring alternative therapy (doxycycline or fluoroquinolones) and a higher rate of pneumonia progression and extrapulmonary complications.[100-102]

Laboratory Diagnosis of MRMP

- Nasopharyngeal secretions or lower respiratory tract specimens (if possible) should be obtained for detection of *M. pneumoniae* by PCR if *M. pneumoniae*-associated CAP is suspected.
- Culture for *M. pneumoniae* and susceptibility testing is not routinely performed.
- Rapid molecular testing for MRMP should be considered directly in respiratory specimens (e.g. nasopharyngeal secretions or lower respiratory tract specimens) positive for *M. pneumonia*e DNA if lack of clinical response after two days of macrolide therapy. Depending on the assay method and testing schedule, results may be obtained within a few hours or after 1-2 days.
- The resistance result could back-up the treatment decision.

Management

- The benefit of targeted antibiotic treatment remains controversial, especially for children with mild to moderate mycoplasma pneumonia. A comprehensive review of the published literature identified insufficient evidence to support or refute treatment of *M. pneumoniae* pneumonia,[103] but commented that findings in published studies may be confounded by subjective outcomes, mixed infections, timing of intervention and diagnostic methods.
- Physicians should consider MRMP if children with *M. pneumoniae*-associated CAP fail to respond to macrolide therapy
- Doxycycline (4 mg/kg/day, twice daily) is recommended for the treatment of MRMP-associated CAP in children >8 years old.[102]
- For children ≤8 years old infected with MRMP-associated CAP, doxycycline should be used when the benefit exceeds risk.
- Fluoroquinolone (e.g. levofloxacin, 8 mg/kg/day, once daily) is an alternative option to doxycycline for MRMP-associated CAP in children ≤8 years old.[102]
- For severe MRMP cases where oral antibiotics cannot be tolerated, intravenous minocycline (4 mg/kg/day.[104] 4 mg/kg/day IV stat, then 2 mg/kg Q12H IV, max 100 mg[105]) could be used.

MRMP was first reported in Japan in 2001.[106] Since then, there has been reports in China,[107-110] South East Asia,[111-113] North America[114,115] and various European countries.[116-118] In China, the prevalence of MRMP is exceptionally high, constituting over 90% of all isolates of *M. pneumoniae*.[108] The first locally acquired case of MRMP in Hong Kong has been reported in the New Territories West cluster in 2010.[119]

The true epidemiology of *M. pneumoniae* and the prevalence of MRMP in Hong Kong remains unclear. There are two local publications providing information on the local situation of MRMP. The first study evaluated different molecular methods to detect genotypic resistance in *M. pneumoniae* in both adult and paediatric subjects.[97] Pyrosequencing identified mutation at the position A2063G in 78.8% of the *M. pneumoniae*-positive samples, and 39% by Sanger sequencing and melting curve analysis. The difference is mainly due to the ability of pyrosequencing to identify low-frequency MRMP quasispecies. Another local study evaluated the antibiotics treatment efficacy against MRMP in the paediatric age group only.[99] Among the paediatric CAP cases with a positive *M. pneumonia*e PCR, 70% were MRMP. Only A2063G mutation was identified in both studies.

If mycoplasma pneumonia is suspected, nasopharyngeal secretions should be tested for *M. pneumoniae* by PCR.[97,100,120] PCR is superior to serology for the diagnosis of acute *M. pneumoniae* infection although nucleic acid may remain detectable for prolonged periods after recovery.[121]

If response to macrolide treatment for presumed mycoplasma pneumonia is lacking, direct rapid genetic testing for MRMP in respiratory specimens positive for *M. pneumoniae* DNA is indicated to guide alternative antibiotic therapy. Currently, real-time PCR of the domain V of the 23s rRNA gene coupled to melting curve analysis is the most widely used method for identification of MRMP in Hong Kong.[97,99,119,122] Genotypic detection of MRMP is available in selected specialised centers, University hospitals and the Government Public Health Laboratory Service in Hong Kong. Since the result of the resistance genotype may not be readily available, empirical initiation of alternative antimicrobial agents may sometimes be required.

Neither IDSA guideline nor BTS guideline have any recommendation on the treatment of MRMP.[3,4] The Japanese guideline for management of respiratory infection in children published in 2007 has recommended the switching to tetracycline antibiotics if fever persists for more than 48 hours after macrolide antibiotic initiation.[123] *In-vitro* studies have demonstrated that the tetracyclines and fluoroquinolones have relatively low MIC value against MRMP.[109,124-126] Several case series in Japan have suggested the use of minocycline and doxycycline for treatment of MRMP in children.[127-129]

Both fluoroquinolones and tetracyclines have the potential to cause toxicities in young children.[130-133] The doctor should explain the reasons for their use and potential side effects to the parents before prescribing the drug.

10. Discharge Criteria for Children Hospitalised with Community-acquired Pneumonia

- Patients are eligible for discharge when they have documented overall clinical improvement, including stable/baseline mental status, level of activity, appetite, consistent pulse oximetry measurements >94% in room air and decreased fever for at least 12-24 hours.
- Patients are not eligible for discharge if they have substantially increased work of breathing or sustained tachypnea or tachycardia.
- Patients should have documentation that they can tolerate their home anti-infective regimen, whether oral or intravenous, and home oxygen regimen, if applicable, before hospital discharge.
- For children who have had a chest tube and meet the requirements listed above, hospital discharge is appropriate after the chest tube has been removed for 12-24 hours, either if there is no clinical evidence of deterioration since removal or if a chest radiograph, obtained for clinical concerns, shows no significant reaccumulation of a parapneumonic effusion or pneumothorax.
- In infants and children with barriers to care, including concern about careful observation at home, inability to comply with therapy, or lack of availability for follow-up, these issues should be identified and addressed before discharge.
- In improving patients who otherwise meet criteria for discharge, a positive blood culture with identification or susceptibility results pending should not routinely preclude discharge of that patient with appropriate oral or intravenous antimicrobial therapy. The patient can be discharged if close follow-up is assured.

Declaration of Interest

The following authors have **NO** interest to declare:
LAM Shu Yan David
LUNG David Christopher
CHAN Eric
CHAN Kwok Chiu
CHIU Susan, Shui Seng
HO Pak Leung
HO Wai Tsun Vincent
LEUNG Chi Wai
LUK Wan
TAM Yat Cheung Alfred

The following author declares that the following condition concerning him or his immediate family members could cause conflict of interest.

WONG Gary
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pneumococcal immunization. J Microbiol Immunol Infect 2016; 49:225-9.
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