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Guideline

Recommendations and guidelines for the treatment of pneumonia in Taiwan

KEYWORDS
Pneumonia;
Guidelines;
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Executive Summary Pneumonia is a leading cause of death worldwide, ranking third both globally and in Taiwan. This guideline was prepared by the 2017 Guidelines Recommendations for Evidence-based Antimicrobial agents use in Taiwan (GREAT) working group, formed under the auspices of the Infectious Diseases Society of Taiwan (IDST). A consensus meeting was held jointly by the IDST, Taiwan Society of Pulmonary and Critical Care Medicine (TSPCCM), the Medical Foundation in Memory of Dr. Deh-Lin Cheng, the Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines. The final guideline was endorsed by the IDST and TSPCCM. The major differences between this guideline and the 2007 version include the following: the use of GRADE methodology for the evaluation of available evidence whenever applicable, the specific inclusion of healthcare-associated pneumonia as a category due to the unique medical system in Taiwan and inclusion of recommendations for treatment of pediatric pneumonia. This guideline includes the epidemiology and recommendations of antimicrobial treatment of community-acquired pneumonia, hospital-acquired pneumonia, ventilator-associated pneumonia, healthcare-associated pneumonia in adults and pediatric pneumonia.

Introduction

Pneumonia is a leading cause of death worldwide, ranking third both globally and in Taiwan, in 2017.[1] Numerous guidelines have been published by various societies in many countries for the treatment of pneumonia, including the United Kingdom,[2,3] United States,[4,5] China,[6] India,[7] South Africa[8] and Europe.[9,10] Development of local guidelines to address the differences in local epidemiology, microbiology and antimicrobial resistance is recommended. The Infectious Diseases Society of Taiwan (IDST) published the first edition of Guidelines on Antimicrobial Therapy of Pneumonia in Adults in Taiwan in 1999,[11] which was revised in 2001 and 2007, in conjunction with the Taiwan Society of Pulmonary and Critical Care Medicine (TSPCCM).[12] In 2014, the Guidelines Recommendations for Evidence-based Antimicrobial agents use in Taiwan (GREAT) working group was formed under the auspices of the IDST, and members were re-appointed annually. The 2017 GREAT working group comprised of infectious diseases physicians representing 13 medical centers across Taiwan and 1 regional hospital, who convened to review the latest global and local evidence on the management of pneumonia, and to form preliminary recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[13] A consensus conference was held in March 2018, to review the evidence and strength of recommendations. The consensus meeting was held jointly by the IDST, TSPCCM, the Medical Foundation in Memory of Dr.

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Deh-Lin Cheng, the Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education and CY Lee's Research Foundation for Pediatric Infectious Diseases and Vaccines. The final guideline was endorsed by the IDST and TSPCCM. These recommendations are intended primarily for use by healthcare professionals who provide care for patients with pneumonia, including primary care practitioners, emergency medicine physicians and specialists in infectious diseases, pulmonary diseases, critical care medicine, and other specialties, to guide and assist clinicians in the management of pneumonia; and not to supersede or replace clinical judgment in consideration of the special circumstances and optimal treatment for each individual patient. Antimicrobial agents included in this recommendation include agents that are currently available in Taiwan.

The major differences between this guideline and the 2007 version include the following: the use of GRADE methodology for the evaluation of available evidence whenever applicable[13,14]; the specific inclusion of healthcare-associated pneumonia (HCAP) as a category due to the unique medical system in Taiwan, where long term care facilities include respiratory care wards (RCW), caring for chronically ventilated patients and hemodialysis (HD) clinics are reimbursed fully by Taiwan's universal national health insurance (NHI). HCAP is further stratified by the risk of multidrug-resistant organisms (MDROs) in subcategories of nursing home acquired pneumonia (NHAP), pneumonia in RCWs and hemodialysis-associated pneumonia (HDAP). Finally, recommendations for treatment of pediatric pneumonia was included.

Epidemiology and recommendations of antimicrobial treatment of CAP, HAP, VAP, HCAP in adults and pediatric pneumonia are discussed in this guideline.

Definition

CAP was defined as a pulmonary parenchymal acute infection in patients who acquire the condition in the community.

HAP was defined an infection of pulmonary parenchyma in patients who acquire the condition at least 48 h after admission to hospital, or within 14 days after discharge from hospital.

VAP was defined as an infection of pulmonary parenchyma occurring at least 48 h after endotracheal intubation.

HCAP was defined as a pulmonary parenchymal infection in patients who was previously hospitalized in an acute care hospital for two or more days within 90 days prior to current infection; resided in a nursing home or long term care facility; received recent intravenous antibiotic therapy within 90 days, chemotherapy, chronic wound care, or HD within 30 days prior to the current infection.[15] The 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) removed the concept of HCAP. In Taiwan, HCAP remains a distinct clinical entity different from CAP and HAP/VAP, due to the unique medical care system, with the existence of numerous RCWs, caring for chronically ventilated patients, and HD clinics, covered by the universal NHI, and recurrent hospitalization of patients in long term care facilities, resulting in a different epidemiology and antimicrobial resistance patterns in this patient population. The category of HCAP was further stratified by risk of MDROs, and subcategorized into two populations with special concern: hemodialysis-associated pneumonia (HDAP) and nursing home-associated pneumonia (NHAP).

Methods

Organization of committee members

A writing group, named the GREAT working group, was appointed in 2017 by the Infectious Diseases Society of Taiwan, with representative members from 13 medical centers in Taiwan, including (by alphabetical order) Chang Gung Memorial Hospital, Kaohsiung; Chang Gung Memorial Hospital, Linkou; Changhua Christian Hospital; Chi Mei Medical Center; China Medical University Hospital; Kaohsiung Medical University Chung-Ho Memorial Hospital; Kaohsiung Veterans General hospital; Mackay Memorial Hospital; National Cheng Kung University Hospital; National Taiwan University Hospital; Shin Kong Wu Ho-Su Memorial Hospital; Taichung Veterans General Hospital; Taipei General Veterans Hospital; Tri-service General Hospital; and 1 regional hospital, Taipei Tzu Chi Hospital.

Grading of recommendations

In this guideline, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system principles were used to guide assessment of the quality of the evidence (very low [D], low [C], moderate [B], and high [A]) and to determine the strength of recommendations (weak [2] or strong [1]).[13,14] Data from randomized controlled trials being as "high" quality, and data from observational studies begin as "low" quality. Five factors are evaluated to lower the quality: risk of bias, inconsistency, indirectness, imprecision and publication bias, and three factors to raise the quality: if the evidence has large effect, dose response, or all plausible confounding and bias. After assessment of the balance between benefit and harm, patient values and preferences, cost and resources, and feasibility and acceptability of the intervention, the strength of recommendations were generated. The GRADE recommendations were classified as strong or weak. A strong recommendation reflects that desirable effects of adherence to a recommendation clearly outweigh the undesirable effects. A weak recommendation reflects that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects. Nevertheless, a strong recommendation does not imply standard of care. In consideration of patient preferences or clinical characteristics that make the recommendation less applicable, strong recommendation cannot or should not be followed for certain individuals.

In this recommendation, each author was assigned to review the literature for a single topic, evaluate the evidence, and determine the strength of the recommendations according to GRADE methodology. All panel members discussed given topics and recommendations during 5 face-to-

face meetings to deliberate the statements and reach a consensus. An outside external panel of experts then reviewed the final guidelines at a consensus meeting. This recommendation was approved by the board members and endorsed by the Infectious Diseases Society of Taiwan and the Taiwan Society of Pulmonary and Critical Care Medicine.

Epidemiology

CAP

The most common causative pathogen for CAP remains *Streptococcus pneumoniae* with a decreasing trend globally.[16,17] Other typical pathogens contributing to CAP include *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. Atypical pathogens including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila* are common causes of CAP.[16,18–22]

In Taiwan, the microbiologic diagnosis can be confirmed in as high as 75% of cases of pneumonia with extensive diagnostic tools.[23–31] The five most significant pathogens for CAP in Taiwan are *S. pneumoniae* (23–26%), *M. pneumoniae* (14–20%), *C. pneumoniae* (8–13%), *H. influenzae* (5–9%), and *K. pneumoniae* (5–7%).[26,32] Age is an important factor affecting the distribution of pathogens in CAP. In patients older than 60 years of age, *S. pneumoniae* is a predominant pathogen of CAP with a prevalence of 28.7%, while *M. pneumoniae* accounts for 19% of CAP in patients younger than 44 years of age.[24] *K. pneumoniae* is a major cause of CAP in patients in the middle age range.[24,26] Other important pathogens causing CAP, include *Pseudomonas aeruginosa*, *S. aureus*, and viruses. In patients with high disease severity, e.g. high pneumonia severity index (PSI) or respiratory failure requiring mechanical ventilation, *K. pneumoniae* and *P. aeruginosa* should be considered.[28,33]

Rare but important pathogens causing CAP in Taiwan include *Burkholderia pseudomallei*, the causative pathogen of melioidosis and rickettsioses, both of which are reportable diseases. About 70% of patients with melioidosis develop pneumonia. Each year, about 50 cases of melioidosis are reported in Taiwan, especially in Southern Taiwan, after typhoons or heavy rainfalls.[34,35] Scrub typhus causes diseases in around 400 patients each year in Taiwan. Pneumonia is diagnosed in 36% of cases. Without adequate treatment, 15% of patients will develop acute respiratory distress syndrome (ARDS).[36] Q fever is reported in 50–100 patients each year, in whom 13.5% may present with pneumonia,[37] and should be considered in patients with a history of animal exposure.

HAP and VAP

The five most common pathogens causing HAP and VAP are *S. aureus*, *Pseudomonas* species, *Acinetobacter* species, *Escherichia* species and *Klebsiella* species,[38,39] which cause nearly 80% of all episodes. Other commonly seen pathogens include *S. pneumoniae*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, and *Enterobacter* species.[5,9,40–42] *S. aureus* ranks first in the causative pathogens, accounting for 36.3% of HAP and VAP in the Unites States and 23% in Europe.[43] In Asia, *S. aureus* is also the most frequent pathogen of HAP and VAP in China and South Korea. In Taiwan, however, *S. aureus* ranks the fourth place as the etiology of HAP/VAP, accounting for only 8% of HAP and VAP.[44,45] *P. aeruginosa* is the most common pathogen in Taiwan, followed by *K. pneumoniae*, *Acinetobacter baumannii*, *S. aureus*, *Enterobacter* species, *S. maltophilia*, and *Escherichia coli*.[44,45]

HAP

The universal NHI coverage in Taiwan enabled accessibility to healthcare, and a large number of aging, diseased or disabled people receive medical care in healthcare facilities. In the face of an ageing population (13.8% of the population in 2017 are over 65 years old), there is an increasing number of elderly people in long term care facilities, and some require frequent, recurrent hospitalizations for health problems. In addition, Taiwan has the highest global incidence and prevalence of treated end-stage renal disease (ESRD) in 2015. The NHI covers HD costs in HD clinics and chronic care of ventilated patients in RCWs. However, the physical and clinical conditions of this population are highly diverse, with varying risk for MDROs. It is recommended to evaluate the risk for MDROs when choosing an optimal treatment regimen for pneumonia in this population. In this guideline, HCAP is further categorized into high and low risk for MDROs, HDAP and NHAP.

HCAP in Taiwan

Data describing the epidemiology and microbiology of HCAP in Taiwan are scarce. A retrospective cohort study in a tertiary hospital in northern Taiwan reported that the most common identifiable pathogen was *P. aeruginosa*, accounting for 25.1% of HCAP.[46] Similarly, in two multicenter, cohort studies recruiting patients from six medical centers, *Pseudomonas* species was the leading pathogen, responsible for 29–32% of HCAP episodes.[47,27] The prevalence of methicillin-resistant *S. aureus* (MRSA) in HCAP patients was low in Taiwan, accounting for only 7–8% of infections.[27,46,47]

HDAP

Patients with ESRD undergoing HD are prone to a wide variety of infection, including pneumonia.[48] The mortality rate for HDAP is higher than that for pneumonia in the general population.[49] The risk factors and microbiological etiology in patients with HDAP were discussed in several studies.[46,23,50,51] *S. aureus*, *K. pneumoniae* and *P. aeruginosa* are the most important pathogens in patients undergoing HD with pneumonia. The distribution of MRSA, however, is variable. Therefore, empirical treatment targeting MRSA is recommended only in patients with severe HDAP.[23,46]

NHAP

Residents of long term care facilities and nursing home with pneumonia are at a higher risk for infection with MDROs

only if they were recently hospitalized or had other comorbidities.[5,15] However, treatment outcome and the mortality is not associated with the presence of MDROs, but more related to the physical conditions of the patients and comorbidities.

In Taiwan, numerous long term care facilities are available, such as nursing homes, which provide care for residents with highly variable physical conditions, ranging from relatively healthy and ambulatory elderly requiring only simple help for daily activities to disabled and bedridden people with long-term catheter placement. Although pneumonia acquired in the nursing home may have a higher risk for infection with MDR pathogens, a retrospective study in South Korea found that the risk was not as high as that for HAP.[52] On the other hand, a study recruiting patients with NHAP and CAP in South Korea indicated that the mortality rate was not associated with the place where pneumonia developed but with the severity of the pneumonia at onset.[53] For NHAP, the disease severity, physical conditions, and comorbidities are more important predictors for mortality than the presence of MDROs.

Risk for infections with MDROs in HCAP

There is no single, independent risk factor to predict infections with MDROs in HCAP. The risk accumulates with multiple risk factors.[54] The development of infection with MDROs is facilitated by previous use of antibiotics because of the resulting selective pressure on pathogens.[55] Moreover, the risk of infection with MDROs may change and vary according to previous exposure to different antibiotics.[56] There is also a temporal relationship between antibiotic exposure and risk of MDROs. The shorter the time between the most recent antibiotics use and the onset of pneumonia, the higher the risk of infection with MDROs.[56] Other risk factors include the presence of microorganisms in the oropharynx and host factors such as risk of aspiration and underlying chronic diseases. Table 6 illustrates the risk factors for MDROs in HCAP.

Pediatric pneumonia

The etiology of CAP in pediatric patients has changed significantly among developing and newly industrialized countries throughout the past two decades.[57] The introduction of *H. influenzae* type b conjugate vaccines (HibCV) and pneumococcal conjugate vaccines (PCV) are two important responsible factors, especially in countries where these two vaccines are included in the national immunization programs (NIP).[58–60]

In Taiwan, HibCV was first introduced in 1996, but not until 2010 was HibCV included in the NIP as part of Diphtheria and tetanus toxoid with acellular pertussis, inactivated polio and *H. influenzae* type b vaccine (DTaP-Hib-IPV vaccine). The 7-valent pneumococcal conjugate vaccine (PCV7) and the 13-valent pneumococcal conjugate vaccine (PCV13) were introduced in 2005 and 2011 respectively. Since 2013, all children aged 2–5 years and since 2014, all children aged 1–5 years were provided with PCV13 via a catch-up immunization program by the NIP. In 2015, the Taiwan Centers for Disease Control (CDC) modified the NIP and initiated routine PCV13 immunization with a "two plus one schedule", which is to prime with two vaccines, one at the age of 2 months and the other at 4 months, and give one booster after 12 months of age.

The surveillance of invasive *H. influenzae* and invasive pneumococcal disease (IPD) was not included in the Taiwan National Notifiable Disease Surveillance System (NNDSS) until 1999 and 2007, respectively. A comprehensive epidemiology of CAP etiology in children is lacking. Two prospective studies investigating the etiology of CAP in children in Taiwan showed that the major pathogen was *S. pneumoniae*. One study recruited children admitted to a medical center in Northern Taiwan in the pre-PCV era between 2001 and 2002 reported that *S. pneumoniae* accounted for 41.1% of 209 children with CAP,[61] while the other study conducted by the Taiwan Pediatric infectious Disease Alliance (TPIDA) included CAP children across pre-PCV and post-PCV era from November 2010 to September 2013 found that in the pre-PCV era, *S. pneumoniae* accounted for about 31.6% of 1032 children with CAP.[62] Different from western countries, these two studies noted that the prevalence of *M. pneumoniae* in children aged younger than 19 years was higher, up to 22.6%[62] and 36.8%[61] in Taiwan. Resistance of *M. pneumoniae* to macrolides reaching 12–23% in Taiwan is a concern.[63–65]

The universal use of the HibCV and PCV in other countries resulted in viral pathogens becoming a predominant cause among infants and preschool children, while the proportion of *M. pneumoniae* infection increased with age.[66,67] The national PCV13 childhood immunization program commenced in 2015 in Taiwan, and with only 3 years of implementation, it may be too early to assess the long-term impact of PCV vaccination on CAP etiology in Taiwan. However, similar changes in the prevalent pathogens may occur in the future, based on the experiences in other countries with a universal PCV program. Further studies regarding local epidemiology are warranted for optimizing management of childhood CAP.

Recommended antibiotics treatment

CAP

Empirical antimicrobial therapy

We used CRB-65 score and CURB-65 score to evaluate the severity of CAP in this guideline. Table 1 lists the recommended choices of antibiotics for empirical treatment of CAP.

Outpatient treatment, low severity (CRB-65 = 0–1)

1. No comorbidities, and no history of antibiotic treatment in the recent 3 months

For patients without comorbidities and recent history of exposure to antimicrobial agents, monotherapy with a β-lactam antibiotic or a non-β-lactam drug for atypical pathogens (mainly for *Mycoplasma* or *Chlamydophila* infection), such as macrolides or tetracyclines, is recommended. The selection of antimicrobial agent depends on

Table 1 Empiric therapy for community-acquired pneumonia in adults.

Disease severity	Disposition	Preferred	Alternative	Treatment duration
Low severity	Outpatient	Amoxicillin 500 mg-1g PO q8h		5–7 days[e]
CRB-65 = 0–1[a]		Amoxicillin/clavulanate 1–2 g PO q12h		
No comorbidities, no history of antibiotic treatment in recent 3 months		Ampicillin/sulbactam 375–750 mg PO q12h		
		Cefaclor 500 mg PO q8h[b]		
		Presumed atypical pathogen		
		Azithromycin 500 mg PO qd		3–5 days[f]
		Clarithromycin 500 mg PO q12h		
		Doxycycline 100 mg PO q12h		
		Minocycline 100 mg PO q12h		
With comorbidities, or history of antibiotic treatment in recent 3 months		Amoxicillin 500 mg -1 g PO q8h	Moxifloxacin 400 mg PO qd[c]	5–7 days[e]
		Amoxicillin/clavulanate 1–2 g PO q12h	Levofloxacin 500–750 mg PO qd[c]	
		Ampicillin/sulbactam 375–750 mg PO q12h	Gemifloxacin 320 mg PO qd	
		Cefaclor 500 mg PO q8h[b]	Nemonoxacin 500 mg PO qd[d]	
		+/–		3–5 days[f]
		Azithromycin 500 mg PO qd		
		Clarithromycin 500 mg PO q12h		
Low severity	Non-ICU	Amoxicillin 500 mg-1 g PO q8h	Moxifloxacin 400 mg PO/IV qd[c]	5–7 days[e]
CURB-65 = 0–1[a]		Amoxicillin/clavulanate 1–2 g PO q12h	Levofloxacin 500–750 mg PO/IV qd[c]	
Hospitalized due to reasons other than disease severity (e.g. living alone, difficult to follow up, or accompanied with other clinical conditions requiring hospitalization.)		Ampicillin/sulbactam 375–750 mg PO q12h		
		Cefaclor 500 mg PO q8h[b]	Gemifloxacin 320 mg PO qd	
		Penicillin G 1–2 MU IV q6h-q4h	Nemonoxacin 500 mg PO qd[d]	
		Ampicillin 1–2 g IV q6h		
		Amoxicillin/clavulanate 1.2 g IV q8h		
		Ampicillin/sulbactam 1.5–3 g IV q6h		
		Cefuroxime 1.5 g IV q8h[g]		
		+/–		
		Azithromycin 500 mg PO QD		
		Clarithromycin 500 mg PO q12h		3–5 days[f]
Moderate severity	Non-ICU	Amoxicillin/clavulanate 1.2 g IV q8h	Moxifloxacin 400 mg IV qd[c]	5–7 days[e]
CURB-65 = 2–3[a]		Ampicillin/sulbactam 1.5–3 g IV q6h	Levofloxacin 500–750 mg IV qd[c]	
		Cefuroxime 1.5 g IV q8h[g]	Tigecycline[i] 100 mg loading, then	
		Ceftriaxone 2 g IV qd	50mg IV q12h	
		Cefotaxime 1–2 g IV q8h	Ceftaroline 500mg IV q12h	
		Ertapenem 1 g IV qd[h]		
		+		
		Azithromycin 500 mg PO qd		
		Clarithromycin 500 mg IV/PO q12h		3–5 days[f]

High severity **CURB-65 = 3–5**[a]	ICU	**β-lactam based combination** Amoxicillin/clavulanate 1.2 g IV q8h Ampicillin/sulbactam 1.5–3 g IV q6h Cefuroxime 1.5g IV q8h[g] Ceftriaxone 2 g IV qd Cefotaxime 1–2 g IV q8h Ertapenem 1 g IV qd[h] **One of the above β-lactam antibiotics plus one of the following macrolides:** Clarithromycin 500 mg IV/PO q12h Azithromycin 500 mg PO qd **or one of the following fluoroquinolones:** Moxifloxacin 400 mg IV qd[c] Levofloxacin 500–750 mg IV qd[c]	7 days[e]
Special considerations			
Risk of *Pseudomonas* infection[j]		Piperacillin/tazobactam 4.5 g IV q8h-q6h Ticarcillin/clavulanate 3.1 g IV q6h Cefoperazone/sulbactam 4 g IV q12h Cefepime 2 g IV q8h Imipenem 500 mg IV q6h–1g IV q8h Meropenem 1 g IV q8h +/− [k] Ciprofloxacin 400 mg IV q8h–12h Levofloxacin 750 mg IV qd Amikacin 15–20 mg/kg IV qd	
Risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection		Vancomycin 15–20 mg/kg IV q8–12h Teicoplanin 6–12 mg/kg/dose IV q12h x 3–5 doses, then 6–12 mg/kg/dose qd Linezolid 600 mg PO/IV q12h	
Risk of aspiration pneumonia and anaerobic infection[l]		Amoxicillin/clavulanate 1–2 g PO q12h Ampicillin/sulbactam 375–750 mg PO q12h Amoxicillin/clavulanate 1.2 g IV q8h Ampicillin/sulbactam 1.5–3 g IV q6h Moxifloxacin 400 mg PO/IV qd[c] Ertapenem 1 g IV qd or metronidazole 500 mg PO/IV q8h plus one of the following β-lactams:	

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Table 1 (*continued*)

Disease severity	Disposition	Preferred	Alternative	Treatment duration
		Cefaclor 500 mg PO q8h[b] Cefuroxime 1.5 g IV q8h[g] Ceftriaxone 2 g IV QD Cefotaxime 1—2 g IV q8h		

[a] In outpatient setting, the simplified CRB-65 score is applied, while CURB-65 score is used in inpatient setting. In CRB-65 score, one point is awarded for each of the following features: confusion, respiratory rate that is equal or greater than 30 breaths/min, blood pressure with systolic of 90 mmHg or less or diastolic of 60 mmHg or less, and 65 years of age or older. CURB-65 score includes all features in CRB-65 score and an extra feature of raised blood urea nitrogen over 19 mg/dL which is also awarded one point

[b] Or other oral second-generation cephalosporins

[c] Empiric treatment with levofloxacin and moxifloxacin for pneumonia may delay the diagnosis of pulmonary tuberculosis and increase the risk of fluoroquinolone resistance. Levofloxacin and moxifloxacin should be cautiously used in patients with risk or suspicion of tuberculosis. On the other hand, gemifloxacin and nemonoxacin both have limited *in vitro* activity against *Mycobacterium tuberculosis*. The impact on tuberculosis by these two new generation quinolones requires further investigation

[d] Nemonoxacin 500 mg once daily for 7—10 days was found effective to treat community-acquired pneumonia in a phase 3, multicenter, randomized control trial.[70]

[e] If afebrile for 48 hours and reached clinical stability. Clinical stability is defined as: body temperature $\leq$ 37.8 °C, heart rate $\leq$ 100 beats/min, respiratory rate $\leq$ 24 breaths/min, systolic blood pressure $\geq$ 90 mmHg, arterial oxygen saturation (SO_2) $\geq$ 90% or partial pressure of oxygen (pO_2) $\geq$ 60 mmHg in ambient air, ability to maintain oral intake, normal mental status (the last two criteria are important for discharge or oral switch decision but not necessarily for determination of nonresponse)

[f] The treatment duration for azithromycin

[g] Or other intravenous second-generation cephalosporins

[h] Among patients with risk of *Enterobacteriaceae* infection (especially those with concerns of extended spectrum β-lactamase (ESBL)-producing strain), and without risk of *P. aeruginosa* infection, ertapenem should be considered

[l] The U.S. Food and Drug Administration issued a Boxed Warning to the tigecycline drug label. It is recommended to consult infectious disease specialist when considering tigecycline use

[j] Risk factors for *P. aeruginosa*: recent hospitalization, frequent ($>$ 4 courses per year) or recent administration of antibiotics (last 3 months), severe disease (FEV1 $<$ 30%), oral steroid use ($>$ 10 mg of prednisolone daily in the last 2 weeks)

[k] *P. aeruginosa* infection may be treated with two antipseudomonal drugs to reduce the chance of treatment failure. When the drug susceptibility test of the pathogen is available, antibiotics regimens should be deescalated to monotherapy

[l] The severity-directed antibiotic scheme mentioned above is also applied in this section.

Table 2 Pathogen-specific therapy for community-acquired pneumonia in adults.

Pathogen	Preferred	Alternative	Duration
Streptococcus pneumoniae			5—7 days[b] or 10—14 days[c]
Penicillin MIC <2 iaeap	Penicillin G 2—3 MU IV q4h Amoxicillin 1 g PO q8h Amoxicillin/clavulanate 1.2 g IV/PO q12 h Ampicillin 2 g IV q6h Ampicillin/sulbactam 1.5—3 g IV q6h	Cefuroxime 1.5 g IV q8h[a] Ceftriaxone 1—2 g IV q12 h Cefotaxime 1—2 g IV q8h Levofloxacin 750 mg IV/PO qd Moxifloxacin 400 mg IV/PO qd Doxycycline 100 mg IV/PO q12 h	
Penicillin MIC ≥2 enici	Choose regimens based on susceptibility test, including cefotaxime, ceftriaxone, fluoroquinolones (levofloxacin or moxifloxacin), vancomycin, linezolid, high-dose amoxicillin (3 g/day) with penicillin MIC ≤ 4 μg/mL		
Staphylococcus aureus			7—14 days[e]
Methicillin susceptible	Oxacillin 2 g IV q4-6 h Cefazolin 2 g IV q8h Flucloxacillin 2 g IV q4h	Amoxicillin/clavulanate 1.2 g IV/PO q8h Levofloxacin 750 mg IV/PO qd Moxifloxacin 400 mg IV/PO qd Vancomycin 15—20 mg/kg IV q8-12 h[d] Teicoplanin 6—12 mg/kg/dose IV q12 h × 3—5 doses, then 6—12 mg/kg/dose qd Clindamycin 600 mg IV/PO q8h	
Methicillin resistant	Vancomycin 15—20 mg/kg IV q8-12 h ± rifampicin Teicoplanin 6—12 mg/kg/dose IV q12 h x 3—5 doses, then 6—12 mg/kg/dose qd ± rifampicin Linezolid 600 mg PO/IV q12 h	TMP-SMX double-strength (DS, 160 mg TMP and 800 mg SMX) 1—2 tabs PO q12-24 h TMP 8—20 mg/kg/day IV, divided q6-12 h	
Mycoplasma pneumoniae	Doxycycline 100 mg IV/PO bid x 7—14 days Minocycline 200 mg PO/IV x 1 dose, then 100 mg PO/IV bid x 7—14 days	Azithromycin 500 mg PO on day 1, then 250 mg PO qd x 4 days Levofloxacin 750 mg PO/IV qd × 7—14 days Moxifloxacin 400 mg PO/IV qd × 7—14 days	Depends on regimen
Chlamydophila pneumoniae	Azithromycin 500 mg PO on day 1, then 250 mg PO qd x 4 days	Clarithromycin 500 mg PO q12 h × 10 days Doxycycline 100 mg IV/PO q12 h × 10 days Levofloxacin 500—750 mg PO/IV qd × 7—10 days Moxifloxacin 400 mg PO/IV qd × 10 days	Depends on regimen
Legionella species	Levofloxacin 750 mg IV/PO qd Moxifloxacin 400 mg IV/PO qd Azithromycin 1000 mg IV day 1, then 500 mg IV/PO qd Clarithromycin 500 mg PO q12 h	Doxycycline 100 mg IV/PO q12 h	7—10 days
Haemophilus influenzae			
β-lactamase (−)	Amoxicillin 1 g PO q8h		7—10 days
β-lactamase (+)	Amoxicillin/clavulanate 1.2 g IV/PO q12 h Cefuroxime 1.5 g IV q8h or other 2nd generation cephalosporins Ceftriaxone 2 g IV qd or other 3rd generation cephalosporins	Ciprofloxacin 400 mg IV/PO q12 h Levofloxacin 750 mg IV/PO qd Moxifloxacin 400 mg IV/PO qd or other fluoroquinolones	

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Table 2 (*continued*)

Pathogen	Preferred	Alternative	Duration
Enterobacteriaceae[f]	Cefotaxime 2 g IV q6-8 h[g] Cefepime 2 g IV q8h[h] Ertapenem 1 g IV qd Imipenem 500 mg IV q6h Meropenem 1 g IV q8h	Piperacillin/tazobactam 4.5 g IV q6h Ciprofloxacin 400 mg IV/PO q12 h Levofloxacin 750 mg IV/PO qd Moxifloxacin 400 mg IV/PO qd	7—10 days
Pseudomonas aeruginosa	**Antipseudomonal β-lactams** Ceftazidime 1—2 g IV q8-12 h Cefoperazone/sulbactam 4 g IV q12 h Cefepime 2 g IV q8h Piperacillin/tazobactam 4.5 g IV q6h Imipenem 500 mg IV q6h-1 g IV q8h Meropenem 1 g IV q8h **plus** **one of the following antibiotics:** Ciprofloxacin 400 mg q12 h Levofloxacin 750 mg qd Amikacin 20 mg/kg/day	Amikacin 20 mg/kg/day + Ciprofloxacin 400 mg q8-12 h Levofloxacin 750 mg qd	7 days
Burkholderia pseudomallei	**Intensive phase**[i,j] Ceftazidime 50 mg/kg (up to 2 g) IV q6h Meropenem 25 mg/kg (up to 1 g) IV q8h Imipenem 25 mg/kg (up to1gm) q8h **Eradication phase** TMP/SMX PO <40 kg: 160/800 mg q12 h; 40—60 kg: 240/1200 mg q12 h; > 60 kg: 320/1600 mg q12 h plus folic acid[m] 0.1 mg/kg up to 5 mg PO qd	Imipenem 25 mg/kg up to 1 g IV q6h Amoxicillin/clavulanate[l] 20/5 mg/kg PO q8h, up to maximum of 1500/375 mg PO q8h plus doxycycline 100 mg PO q12 h	14 days[k] ≥3 months

[a] Or other intravenous second-generation cephalosporins
[b] If patients are afebrile for at least 48 h and has no more than one CAP associated signs of clinical instability
[c] If accompanied with *S. pneumoniae* bacteremia
[d] It is recommended to give vancomycin at an interval of q6h in immunocompromised patients
[e] Longer course of up to 4 weeks may be considered if *S. aureus* bacteremia presents
[f] With *E. coli*, *K. pneumoniae* and *Proteus mirabilis* infection, antibiotic regimens should be de-escalated to first or second-generation cephalosporins according to the susceptibility test once it is available
[g] Or other intravenous third-generation cephalosporins
[h] Or other intravenous fourth-generation cephalosporins
[i] If patients present with septic shock, granulocyte colony-stimulating factor (G-CSF) 300 μg IV for 10 days may be considered
[j] If the infections involve central nervous system, TMP/SMX 8/40 mg/kg (up to 320/1600 mg) IV/PO q12 h should be added
[k] Longer duration (4—8 weeks or longer) should be administered if patients are critically ill, have extensive pulmonary disease, deep seated collections or organ abscesses, osteomyelitis, septic arthritis, or neurologic melioidosis
[l] For patients who are allergic to sulfonamide
[m] Folic acid is given to prevent or reduce the antifolate activity of TMP/SMX without affecting its antimicrobial activity.

Table 3 Risk factors for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) caused by multidrug-resistant organisms (MDROs).

Septic shock at time of HAP/VAP
Adult respiratory distress syndrome preceding HAP/VAP
Acute renal replacement therapy prior to HAP/VAP onset
Previous colonization of MDROs
Structural lung diseases (e.g. bronchiectasis).

the patient's clinical manifestations and contact history. It should be noted that the susceptibility rate of *S. pneumoniae* to azithromycin was reported to be low in Taiwan.[68,69] Fluoroquinolones are listed as an alternative choice.[70]

2. With comorbidities, or history of antibiotic treatment in the recent 3 months

For patients with comorbidities or recent history of exposure to antimicrobial agents, β-lactam monotherapy with or without addition of a macrolide are both optimal choices. Fluoroquinolones are listed as an alternative choice.[70] Decision depends on the physician's clinical judgment, based on the individual patient's condition.

Inpatient, non-intensive care unit (ICU) admission, with low severity (CURB-65 = 0–1)

For patients admitted not primarily for the treatment of pneumonia, but for other medical concerns, e.g. multiple comorbidities, single elderly incapable of self-care, disabled patients who are unable to follow up at outpatient clinics, the recommended empirical antibiotics regimen is similar to those for the outpatient group. Intravenous antibiotics may be used for patients with gastrointestinal discomfort or malabsorption.

Inpatient, non-ICU admission, with moderate severity (CURB-65 = 2–3)

For CAP patients with moderate severity and CURB-65 score ≥ 2, we recommend combination therapy with a β-lactam antibiotic and a macrolide (1B). A fluoroquinolones (FQ) is listed as an alternative. Use of intravenous tigecycline is found to be associated with increased all-cause mortality compared to the control in a meta-analysis of phase III and IV clinical trials.[71] The U.S. Food and Drug Administration issued a boxed warning to the tigecycline drug label. Consultation of an infectious disease specialist is recommended when considering tigecycline use.[72]

Table 4 Empiric therapy for hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in adults.

Host/Risk factors	Preferred agents
Low risk of MDRO, stable hemodynamics	**Single antipseudomonal antibiotic**
	Piperacillin/tazobactam 4.5 g IV q6h
	Cefoperazone/sulbactam 4 g IV q12 h
	Ceftazidime 2 g IV q8h
	Cefepime 2 g IV q8h
	Imipenem 500 mg IV q6h
	Meropenem 1 g IV q8h
	Levofloxacin 750 mg IV qd
	Ciprofloxacin 400 mg IV q8h
High risk of MDRO and/or unstable hemodynamics	**Two antipseudomonal antibiotics from different classes**
	Piperacillin/tazobactam 4.5 g IV q6h
	Cefoperazone/sulbactam 4 g q12 h
	Ceftazidime 2 g IV q8h
	Cefepime 2 g IV q8h
	Imipenem 500 mg IV q6h
	Meropenem 1 g IV q8h
	+
	Levofloxacin 750 mg IV qd
	Ciprofloxacin 400 mg IV q8h
	Gentamicin 5–7 mg/kg IV qd
	Amikacin 15–20 mg/kg IV qd
	Colistin 5 mg/kg IV × 1 dose then 2.5mg × (1.5 × CrCl + 30) IV q12h
High risk of MRSA infection	**Gram-negative pathogen coverage as mentioned above plus:**
	Vancomycin 25–30 mg/kg coverage as mentioned abo q8-12 h
	Teicoplanin 6–12 mg/kg IV q12 h × 3 doses then 6-12mg/kg IV qd[a]
	Linezolid 600 mg IV q12 h

MDROs = multidrug-resistant organisms.

[a] A high dose of teicoplanin (12 mg/kg) should be considered in patients with severe disease, concomitant deep-seated infection, or in settings where the MIC values of MRSA to glycopeptides are relatively high.

Table 5 Pathogen-specific therapy for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) in adults.

Pathogen	Preferred agents
Pseudomonas aeruginosa	
Stable hemodynamic status	Piperacillin/tazobactam 4.5 g IV q6h Cefoperazone/sulbactam 4 g IV q12 h Ceftazidime 2 g IV q8h Cefepime 2 g IV q8h Imipenem 500 mg IV q6h Meropenem 1 g IV q8h Levofloxacin 750 mg IV qd Ciprofloxacin 400 mg IV q8h
Unstable hemodynamic status	Piperacillin-tazobactam 4.5 g IV q6h Cefoperazone/sulbactam 4 g IV q12 h Ceftazidime 2 g IV q8h Cefepime 2 g IV q8h Imipenem 500 mg IV q6h Meropenem 1 g IV q8h + Levofloxacin 750 mg IV qd Ciprofloxacin 400 mg IV q8h Gentamicin 5—7 mg/kg IV qd Amikacin 15—20 mg/kg IV qd Colistin 5 mg/kg IV × 1 dose then 2.5 mg × (1.5 × CrCl + 30) IV q12 h
Acinetobacter species	
Not only sensitive to polymyxin and stable hemodynamic status	Ampicillin/sulbactam 3 g IV q6h Imipenem 500 mg IV q6h[a] Meropenem 1 g IV q8h[a]
Sensitive only to polymyxin or unstable hemodynamic status	Colistin 5 mg/kg IV × 1 dose then 2.5 mg × (1.5 × CrCl + 30) IV q12 h +/− one of the following antibiotics: Imipenem 500 mg IV q6h[a] Meropenem 1 g IV q8h[a] Ampicillin/sulbactam 3 g IV q6h + Adjunctive inhaled colistin: daily dose 1.25—15 MIU[b] divided in q8-12 h, each dose diluted in 5 mL sterile normal saline
Carbapenem-resistant pathogens	
Sensitive only to polymyxin Stable hemodynamic status	Colistin 5 mg/kg IV×1 dose then 2.5 mg × (1.5 × CrCl + 30) IV divided in q12 h +/− one for the following antibiotics: Imipenem 500 mg IV q6h[a] Meropenem 1 g IV q8h[a] Ampicillin/sulbactam 3 g IV q6h + Adjunctive inhaled colistin: daily dose 1.25—15 MIU[b] divided in q8-12 h, each dose diluted in 5 mL sterile normal saline
Unstable hemodynamic status	Colistin 5 mg/kg IV×1 then 2.5 mg × (1.5 × CrCl + 30) IV q12 h +/− one of the following antibiotics: Imipenem 500 mg IV q6h Meropenem 1 g IV q8h + Adjunctive inhaled colistin: daily dose 1.25—15 MIU[b] divided in q8-12 h, each dose diluted in 5 mL sterile normal saline

CrCl = Creatinine clearance; MIU = million units.
[a] Extended infusion of carbapenems may be appropriate
[b] 2 MIU colistin methanesulfonate = 66.8 mg colistin base.

Table 6 Definition and risk for multidrug-resistant organisms (MDROs) for healthcare-associated pneumonia (HCAP).

Definition of HCAP
Received intravenous antibiotics within 90 days
Received long-term hemodialysis within 30 days
Received chemotherapy or chronic wound care
Recent hospitalization for more than 48 h with 90 days
Risk for MDROs
Received intravenous antibiotics within 90 days
Recent hospitalization for more than 48 h with 90 days
Reside in nursing home or long-term care facility with high prevalence of MDROs
Risk of aspiration and prior oropharyngeal colonization with MDROs
Long-term outpatient hemodialysis

HCAP = healthcare-associated pneumonia; MDROs = multidrug resistant microorganisms.

Two recent randomized controlled trials (RCTs) for treatment of CAP reported no differences in mortality, complications or length of hospital stay between groups treated with β-lactam monotherapy versus combination therapy with a β-lactam and a macrolide.[73,74] An open-label, multicenter, noninferiority, RCT of monotherapy vs combination therapy, with the primary outcome of reaching clinical stability at day 7, failed to demonstrate non-inferiority for β-lactam monotherapy compared to combination therapy. A planned subgroup analysis found a significant delay in reaching clinical stability for patients receiving β-lactam monotherapy infected with atypical pathogens, and a nonsignificant delay in patients with moderate to high severity (PSI category IV or CURB-65 score $\geq$ 2) pneumonia. A significantly higher 30-day readmission rate was observed.[73] A meta-analysis including these two RCTs and another 12 observational studies showed that addition of a macrolide to a β-lactam had a favorable outcome in severe CAP with PSI category $\geq$ IV or CURB-65 score $\geq$2. Based on the above evidence, it is recommended that combination of a β-lactam with a macrolide should be used in CAP patients with moderate to high severity score (PSI category $\geq$ IV or CURB-65 score $\geq$2). But in patients with a low severity score (CURB-65 score 0—1), β-lactam monotherapy is non-inferior to β-lactam plus macrolide combination therapy.

Inpatient, ICU admission, with high severity (CURB-65 = 4—5)

For patients with high disease severity requiring ICU admission, we recommend combination therapy with a β-lactam plus either a macrolide or a FQ (Table 1). In this group of patients, there is no good evidence to confirm which of these two combinations is more efficacious (2D). Two recent meta-analysis analyzed 17[75] and 8[76] observational studies recruiting 16,684 and 3873 patients, respectively, to compare β-lactam monotherapy and β-lactam plus FQ combination treatment in severe CAP patients. Both meta-analysis found a higher mortality rate in the β-lactam plus FQ group than the β-lactam monotherapy group. However, more than half of the included studies in both meta-analyses had a high risk of bias. The populations were heterogeneous, and only 11 out of the total 25 studies included patients admitted to the ICU. Therefore, the level of evidence is too low to draw a convincing conclusion.

Special consideration

For patients with risks of *P. aeruginosa* or MRSA infection, or with consideration of aspiration pneumonia with anaerobic infection, please refer to the "Special consideration" in Table 1.

The incidence of *P. aeruginosa* in CAP is low.[20,77—79] The risk factors for *P. aeruginosa* include recent hospitalization, frequent (>4 events per year) or recent administration of antibiotics (last 3 months), severe chronic pulmonary disease (FEV1 < 30%) and oral steroid use (>10 mg of prednisolone daily in the last 2 weeks).[80,81] In patients with risk factors for *P. aeruginosa*, an antipseudomonal β-lactam plus either an antipseudomonal FQ (ciprofloxacin or levofloxacin) or an aminoglycoside is preferred.

Empirical treatment for CAP with FQ may delay the diagnosis of pulmonary tuberculosis (TB) and increase the risk of FQ resistance in *Mycobacterium tuberculosis*. FQ should be avoided in patients with risk or suspicion of TB infection (2C). In 2015, the estimated incidence rate of TB in Taiwan was 45.7 per 100,000 people, and the incidence of TB presenting as CAP is 1%. Two meta-analyses including 9[82] and 6[83] retrospective studies indicated that use of FQ prior to TB diagnosis caused a higher risk for FQ resistance. Delayed diagnosis of pulmonary TB with a mean duration of 19.0 days was found in the FQ-exposed group.[82] Hence, for patients with clinical suspicion of TB infection, a discreet review of chest x-ray and medical history is essential. Empirical use of FQ should be cautious in these patients and diagnosis of TB should be diligently sought.

Pathogen-specific therapy

Gram-positive cocci and atypical pathogens

1. *S. pneumoniae*

Penicillin-susceptible *S. pneumoniae* can be treated with β-lactam antibiotics, including penicillin, a penicillin derivative, or a second- or third-generation cephalosporin (Table 2). FQ and doxycycline are alternative choices for patients who are allergic to β-lactams. Currently, well-conducted randomized control trials (RCTs) comparing the efficacy of β-lactams and FQs in treating penicillin-susceptible pneumococcal pneumonia are lacking. For resistant strains, the choice of antimicrobial agents should be based on the results of susceptibility test.

For patients with bacteremic pneumococcal pneumonia or with hypotension or respiratory failure, combination therapy is recommended.[84—87] A significantly lower 14-day mortality with combination therapy (combination versus monotherapy: 8.2 versus 23.1%, respectively, $p = 0.03$) was found in critically ill patients in a prospective, observational study.[86] Further, when comparing combination

therapy that including a β-lactam and β-lactam monotherapy, the mortality was also much lower in β-lactam containing combination therapy group (26.8% versus 58.4%, $p = 0.004$).

There is limited evidence regarding the appropriate duration of antibiotic therapy for pneumococcal pneumonia. The majority of current guidelines recommend 5—7 days for patients with uncomplicated pneumonia and a good clinical response to treatment. For patients with bacteremic pneumococcal disease, antimicrobial therapy should be used for at least 10—14 days, and it is important to ensure that there are no metastatic complications (meningitis, endocarditis, septic arthritis, or empyema) before discontinuation.

2. *S. aureus*

In patients with CAP, if a sputum culture reveals methicillin-susceptible *S. aureus* (MSSA), oxacillin, flucloxacillin or 1st generation cephalosporin is the preferred regimen. For treatment of MRSA, a glycopeptide (vancomycin or teicoplanin) or a linezolid is recommended. In subgroup analysis of MRSA eradication in a meta-analysis of nine randomized trials recruiting pneumonia patients, the rates of mortality and clinical response between linezolid and vancomycin groups were not statistically different.[88] When vancomycin is used, a target trough serum concentration between 15 and 20 μg/mL should be achieved.[89]

One concern with vancomycin is the emergence of increasing minimum inhibitory concentrations (MICs) of MRSA in recent years. Thus, in patients with a MRSA isolate with an increased vancomycin MIC (>2 μg/mL), we recommend the use of linezolid.[89,90] Another issue is toxin production, especially by community-acquired MRSA (CA-MRSA). Vancomycin does not decrease toxin production, whereas linezolid has been shown to reduce toxin production in experimental models.[91,92]

3. *M. pneumoniae*

M. pneumoniae is a common pathogen of community-acquired atypical pneumonia, and it does not usually lead to severe disease, e.g. severe dyspnea or high fever. The antimicrobial therapy for possible *M. pneumoniae* infection includes macrolides (azithromycin or clarithromycin), tetracyclines (doxycycline or minocycline), or FQ (levofloxacin or moxifloxacin). Some trials that evaluated the treatment of CAP including those caused by *M. pneumoniae* reported good efficacy of azithromycin,[93] levofloxacin,[94] and moxifloxacin.[95] However, increased macrolide resistance is reported in some areas, especially in Asia. In China, up to 95% of *M. pneumoniae* isolates from adult patients with respiratory tract infections was resistant to macrolides in one study.[96]

4. *C. pneumoniae*

When a microbiologic etiology of *C. pneumoniae* is confirmed in a patient with CAP, azithromycin is the preferred therapy. FQ, other macrolides, and tetracyclines can be used as alternatives. No clinical trial was found to evaluate the clinical outcomes of CAP in adults infected with *C. pneumoniae*, but several clinical trials showed that a 5-day course of azithromycin had a good *C. pneumoniae* eradication rate at about 80% in nasopharynx.[97,98] The eradication rate of *C. pneumoniae* is about 70—100% with a 10-day course of clarithromycin, erythromycin and moxifloxacin and a 7—10-day course of levofloxacin.[99—101] However, the relationship between the microbiological eradication rate and the clinical outcome is unknown.

5. *Legionella* species

Newer macrolides, especially azithromycin[102—104] and respiratory FQs, especially levofloxacin[94,105] are effective for treatment of *Legionella* infection. To date, RCTs that directly compare the efficacy of macrolides and FQs are lacking. In four observational studies that included nearly 600 patients with Legionnaires' disease, clinical outcomes were similar in patients who received FQs (levofloxacin, ofloxacin, and ciprofloxacin) compared to those with macrolides (erythromycin, clarithromycin).[106—109] However, more rapid defervescence, fewer complications, and shorter hospital stay were associated with the use of FQ. The recommended total duration of antibiotics therapy for *Legionella* pneumonia is 7—10 days. A longer antibiotic course of 21 days may be considered for immunosuppressed patients who are severely ill at presentation.

The clinical benefit of rifampin combination therapy in the treatment of *Legionella* pneumonia remains inconclusive based on currently available evidence. Rifampin therapy may be considered only for patients with severe disease or significant comorbid conditions (e.g. uncontrolled diabetes, smoking, or obstructive lung disease), and immunocompromised hosts or those refractory to conventional monotherapy regimens.[110]

Gram-negative bacilli

1. *H. influenzae*

Amoxicillin and ampicillin should be used only when susceptibility is known, since up to 25—50% of non-typeable strains may produce β-lactamase.[111] A second or third generation cephalosporin or fluoroquinolone is recommended for treatment of β-lactamase producing *H. influenzae*. In a study of clinical isolates from ICUs in Taiwan, high rates of susceptibility were found for cefuroxime, cefixime, cefpodoxime, cefotaxime, amoxicillin-clavulanate.[111] Non-β-lactamase producing and ampicillin-resistant (NBLAR) *H. influenzae* was increasing in Japan and Europe, but was rare in Taiwan (0—8.3%).[111,112] However, levofloxacin resistance in *H. influenzae* has increased significantly in Taiwan, from 2.0% in 2004 to 24.3% in 2010 ($p < 0.001$), in the Taiwan Surveillance of Antimicrobial Resistance (TSAR) study.[113]

2. *M. catarrhalis*

M. catarrhalis has high rates of ampicillin resistance due to β-lactamase production. In a study done in Taiwan, up to 97.8% of clinical isolates produced β-lactamase.[114] All isolates were susceptible to amoxicillin/clavulanate,

cefixime, ciprofloxacin, levofloxacin and moxifloxacin. Recommended treatment is the same as for β-lactamase producing *H. influenzae* (Table 2).

3. *Enterobacteriaceae*

In Asia, the most common Gram-negative bacillus (GNB) causing CAP was *K. pneumoniae* (6.3%).[32] In Taiwan, *K. pneumoniae* is the predominant cause of CAP with bacteremia, and bacteremic pneumonia due to *K. pneumoniae* has a higher mortality rate than bacteremic *S. pneumoniae* pneumonia.[115] There are limited evidences regarding optimal therapy for CAP with *Enterobacteriaceae* infection. In a multicenter, randomized study, in adult patients with moderate-to-severe CAP, the treatment effect of ertapenem 1 g once daily was equivalent to ceftriaxone 1 g once daily for CAP due to *Enterobacteriaceae*, including *Klebsiella* species, *E. coli*, or *Enterobacter* species.[116] Also, ertapenem was as efficacious as cefepime in treating pneumonia with *Enterobacteriaceae* infection.[117] Table 2 lists the recommended regimens for CAP due to *Enterobacteriaceae*.

4. *P. aeruginosa*

Two antipseudomonal antibiotics is empirically used to treat CAP due to *P. aeruginosa* because of the risk of non-susceptibility to a single antipseudomonal agent. When the susceptibility result is available, combination treatment may be de-escalated to monotherapy.[118]

5. *B. pseudomallei* (Melioidosis)

B. pseudomallei is inherently resistant to penicillin, ampicillin, first- and second-generation cephalosporins, gentamicin, streptomycin, and polymyxin.[119] Although most strains showed *in vitro* susceptibility to newer β-lactams including amoxicillin/clavulanate, piperacillin, ceftriaxone, cefotaxime, ceftazidime, imipenem and meropenem,[120–123] a higher overall mortality rate was found in those treated with ceftriaxone or cefotaxime compared with ceftazidime.[122,123] The treatment of melioidosis starts with an intensive phase of at least 14 days of ceftazidime, meropenem, or imipenem. Patients with critical illness, extensive pulmonary disease, deep-seated collections or organ abscesses, osteomyelitis, septic arthritis, and neurologic melioidosis required longer intensive treatment. In 1989, an open-label, randomized trial showed that ceftazidime treatment was associated with a 50% lower overall mortality than conventional treatment with a combination of chloramphenicol, doxycycline, trimethoprim (TMP), and sulfamethoxazole (SMX).[124] Compared with ceftazidime, high dose imipenem (50 mg/kg/d) showed no differences in overall survival rates but fewer treatment failure rates.[125] But for severe melioidosis, an observational study showed that meropenem had better clinical outcomes than ceftazidime.[126]

After an initial intensive phase therapy, a subsequent eradication phase therapy is considered necessary for preventing recrudescence or later relapses of melioidosis. TMP-SMX was considered the drug of choice for melioidosis in the eradication phase. The recurrence rate after 20 weeks of oral TMP-SMX monotherapy was not higher than that of a combination of TMP-SMX plus doxycycline.[127] Amoxicillin/clavulanate and doxycycline were recommended as alternatives for eradication phase therapy if TMP-SMX was intolerated or contra-indicated.[128,129] The recommended duration for eradication phase is 3–6 months.

Time-out and de-escalation

Antibiotics timeout

Patients who are afebrile for 48 h, and reach clinical stability, 5- to 7-day treatment course is safe and effective for mild to moderate severity CAP (1B). For high severity CAP, 7-day treatment course is safe and effective (2C). A longer treatment course is recommended for patients with certain infections, such as MRSA or *B. pseudomallei* (Table 2). Clinical stability is defined as having a body temperature $\leq$37.8 °C, heart rate $\leq$100 beats/min, respiratory rate $\leq$24 breaths/min, systolic blood pressure $\geq$90 mmHg, arterial oxygen saturation (SO_2) $\geq$ 90% or partial pressure of oxygen (pO_2) $\geq$ 60 mmHg in ambient air, and ability to maintain oral intake and normal mental status.[4] The last two criteria are important for decisions to discharge or oral switch but not necessarily for determining nonresponse.

Many RCTs show that 5–7 days of antibiotic treatment course is safe, and as effective as a longer course. Two meta-analyses of 15 and 7 RCTs that compared treatment courses of $\leq$7 days versus >7 days[130] and 3–7 days versus 7–10 days,[131] respectively. Both studies showed no differences in safety and effectiveness between the two treatment duration groups. The most recent multicenter RCT enrolling 312 patients in Spain indicated that a minimum of 5-day treatment course can be implemented safely in hospitalized patients with CAP if they met the clinical stability criteria defined in the Infectious Diseases Society of America/American Thoracic Society guideline.[4] More than one third (38.8%) of the enrolled group were PSI category IV-V and severely-ill patients. However, this trial excluded immunocompromised patients, nursing home residents, pathogens that require a longer duration of therapy (such as *P. aeruginosa* or *S. aureus*, etc.), and other complicated infections such as infective endocarditis, meningitis or empyema. Besides, many patients (nearly 80%) in the study received quinolone as antibiotics treatment.[132]

A review of the subgroup meta-analysis on the RCT conducted in Spain, 2016[132] and the two meta-analyses mentioned above was done,[130,131] and found that there is no difference in clinical success of CAP patients treated with a course of $\leq$7 day and >7 day (RR 1.03, 95% confidence interval [CI]: 0.99–1.08, $p = 0.15$), regardless of the antibiotics regimens and the route of administration (RR 1.01, 95% CI: 0.98–1.05, $p = 0.49$). An observational study including CAP patients with high severity also reported no differences in primary and secondary outcomes between a $\leq$7 day and >7 day treatment course among 328 patients with a CURB score 3–5.[133]

Switch to oral administration

Early intravenous-to-oral antibiotic switch is preferred If patients reached clinical stability. For patients with CAP, regardless of the disease severity, early oral antibiotic switch within 2—4 days is safe and effective (1B).

Many RCTs have demonstrated that early oral antibiotics switch is as safe and effective as longer intravenous treatment. A meta-analysis including 6 RCTs (1219 patients) concluded that a 2-to-4 day early oral switch antibiotic treatment strategy has no differences in clinical success rate, mortality rate or recurrence rate compared to continuing intravenous treatment.[134] A subgroup meta-analysis was conducted to evaluate the clinical outcomes of early oral switch with different antibiotics regimens. It was found that there is no difference in clinical success between use of β-lactams and FQs (RR 0.97 vs 1.03, $p = 0.38$), for subgroup differences.

HAP and VAP

Empirical antimicrobial therapy

Selection of empirical antimicrobial therapy for HAP and VAP should be based on the clinical status of patients, the likelihood of infection with MDROs (Table 3), local distribution of pathogens and their antimicrobial susceptibilities (Table 4).

Stable hemodynamic and low risk for MDROs

Use of one antipseudomonal antibiotic in HAP or VAP patients who have stable hemodynamics and low risk for infection with MDROs is recommended.[5,9] Agents with activity against *L. pneumophila*, e.g. FQs may be considered in units where the prevalence of legionellosis is high.

Unstable hemodynamics, high mortality risk, and/or high risk for MDROs

Two antipseudomonal agents selected from different antibiotics classes is recommended for treatment of patients with HAP or VAP and unstable hemodynamics or high mortality risk, and/or a high risk for MDRO infection.[5,9]

A systematic review of RCTs that compared empiric monotherapy and combination therapy for VAP failed to disclose any statistical differences in mortality, clinical cure and adverse effects.[135] However, these studies did not identify patients with increased risk for MDROs or unstable hemodynamics. It is recommended that the decision for empiric monotherapy or combination antibiotic therapy should be based on individual patient's clinical condition and local antimicrobial resistance data.

Colistin is not recommended for routine empirical antibiotics use, but should be reserved for patients with a high risk of MDROs, prior detection of MDR *Acinetobacter* species, or carbapenem-resistant pathogens.[5,9]

Because the prevalence of MRSA infection in HAP and VAP is low in most hospitals in Taiwan,[44,45] we do not recommend routine empirical use of antimicrobial agents against MRSA in patients with HAP and VAP. If patients are at high risk of MRSA infection, e.g. history of MRSA acquisition or admission to a unit where MRSA accounts for more than 20% of *S. aureus* isolates, empiric anti-MRSA treatment may be considered.[5]

Pathogen-specific therapy

1. *P. aeruginosa*

Choice of antibiotics for treatment of *P. aeruginosa* in HAP or VAP should be based on the antimicrobial susceptibility test. For patients with stable hemodynamic status, monotherapy is recommended. For those with unstable hemodynamics, combination therapy with two antipseudomonal antibiotics from different antibiotics classes is recommended (Table 5).

2. *Acinetobacter* species

In patients with HAP or VAP, with stable hemodynamics and infection with non-MDR *Acinetobacter* species, the use of a single antibiotic according to microbiological susceptibility as listed in Table 5 is recommended.[5]

If patients have unstable hemodynamic status or the isolates are only sensitive to polymyxins, intravenous plus inhaled polymyxins is recommended.[5] Combination treatment with ampicillin/sulbactam, imipenem or meropenem may also be considered.[136,137] A randomized trial found that addition of a carbapenem showed no difference in the clinical outcomes for HAP/VAP due to carbapenem-resistant *Acinetobacter* species. However, the MICs of carbapenem on *Acinetobacter* species in this study were high (MICs > 2 μg/mL), and only half of the recruited patients had pneumonia.[137] Further study is needed to provide conclusive evidence for treatment recommendations.

3. Carbapenem-resistant pathogens

Most carbapenem-resistant pathogens have *in vitro* susceptibility only to polymyxins. In patients with stable hemodynamics, intravenous plus inhaled polymyxin use is recommended.[5] For patients with unstable hemodynamics, intravenous plus inhaled polymyxins, with combined treatment using either imipenem or meropenem is recommended, particularly in patients with critical illness.[138] A randomized study showed no difference in the clinical outcomes after adding a carbapenem to treat carbapenem-resistant Gram-negative bacteria. But most of the pathogens in this study were *Acinetobacter* species, and half of the included patients had diagnosis other than pneumonia.[137] More studies are required to determine whether there is a clinical impact in combination therapy using carbapenems.

Time-out and de-escalation

In HAP and VAP, a 7-day treatment course had similar outcomes compared to a longer treatment course. In contrast, two meta-analyses of RCTs showed that longer treatment in HAP/VAP may increase the risk of infection with drug resistant microorganisms. However, the recurrence rate may be higher if patients with VAP caused by non-fermenting Gram-negative bacilli (e.g. *P. aeruginosa* and *A. baumannii*) received a 7-days treatment course.[139,140] However, most of the studies excluded patients with immunosuppression and structural lung

diseases. Treatment should be individualized, and longer treatment course may also be considered in patients with inappropriate initial empirical therapy.[9]

De-escalation to a narrow spectrum antibiotics is recommended. A retrospective study showed no difference in mortality in the groups with de-escalation compared to maintenance in VAP, while other observational studies had inconsistent results.[141] Owing to the emergence of antibiotic resistance and the principles of antimicrobial stewardship, de-escalation is recommended. For oral antibiotics administration, early switch to oral antibiotics in clinically improving patients after 2—4 days of intravenous antibiotics was also demonstrated to be safe and effective.[100]

HCAP

We recommend stratification of risk in HCAP and treat as CAP or HAP according to the risk for MDROssss or other pathogens. Several factors should be considered in the choice of empirical antimicrobial therapy in HCAP patients, including the risk for MDROs (Table 6), whether patients are undergoing hemodialysis, risk of infection with atypical pathogens and risk of aspiration pneumonia (Table 7). For pathogen-specific therapy, please refer to pathogen-specific therapy for CAP, HAP and VAP in Table 2 and Table 5.

Pediatric pneumonia

Criteria for hospitalization

There is currently no validated scoring system available to guide the decision for hospitalization in pediatric pneumonia. However, most experts and professionals recommend that any child or infant with respiratory distress should be admitted for management (Tables 8 and 9). Hypoxemia is well established as a risk factor for poor outcome in children with respiratory disease. In pediatric patients with non-severe pneumonia, a measurement of saturation <90% using pulse oximetry at the initial visit was predictive of outpatient treatment failure.[142] We recommend to measure oxygenation in all pediatric pneumonia.

Currently, there is a consensus that admission is indicated in a previously healthy child with CAP and an oxygen saturation of <92% in ambient air.[143] Significant comorbidities, such as immunologic disorders, hematologic disorder, cardiac and chronic pulmonary conditions are both risk factors for the development of pneumonia in children and may exacerbate pneumonia and vice versa.[144,145] Hospitalization is recommended for careful evaluation.

Younger age is a risk factor for higher severity in pediatric pneumonia. Age younger than 6 months was one of the most important clinical predictors of treatment failure in children with severe pneumonia in the Amoxicillin Penicillin Pneumonia International Study (APPIS) trial.[146] Mortality is also increased with younger age in children, especially for those under 6 months of age.[147] We recommend all children aged younger than 6 months should be hospitalized for inpatient care.

Other considerations for hospitalization include dehydration, vomiting and inability to take oral medication. Children who fail to respond to oral antimicrobial treatment at outpatient clinic or have progressive respiratory

Table 7 Antimicrobial therapy for healthcare-associated pneumonia (HCAP).

Empirical antimicrobial therapy	
Special consideration	
Low risk for MDROs	Treat as CAP
High risk for MDROs	Treat as HAP/VAP
Hemodialysis-associated pneumonia	**For severe cases** Consider risk for methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*
Atypical pathogens	Include influenza virus and *Legionella* species
Aspiration pneumonia	Cover anaerobic pathogens
Pathogen-specific therapy	
Refer to pathogen-specific therapy for CAP and HAP/VAP	

CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; VAP = ventilator-associated pneumonia; HCAP = healthcare-associated pneumonia.
MDROs = multidrug resistant microorganisms.

Table 8 Criteria for hospitalization in children with pneumonia.

Hypoxemia (oxygen saturation < 92%, cyanosis)
Moderate to severe respiratory distress
Dehydration or inability to feed
Inability of the family to provide appropriate observation or supervision.
Those who with comorbid conditions, such as immunologic disorders and hematologic, cardiac, and chronic pulmonary conditions, cardiopulmonary condition or neurological disease
Outpatient antibiotic treatment failure
Young age (<6 months)
Toxic signs[a]

[a] Toxic signs include but not limit to paleness, cyanosis, general malaise, lack of energy, irritability, conscious disturbance and cognitive function impairment.

Table 9 Signs of respiratory distress in children.

Tachypnea, respiratory rate (breaths/min)	
Age 0—2 months	>60 breaths/min
Age 2—12 months	>50 breaths/min
Age 1—5 years	>40 breaths/min
Age >5 years	>20 breaths/min
Dyspnea	
Retractions (suprasternal, intercostal, or subcostal)	
Grunting	
Nasal flaring	
Apnea	
Altered mental status	
Pulse oximetry measurement < 92% at room air	

Table 10 Empiric therapy for outpatient treatment of community-acquired pneumonia (CAP) in children.[a]

Age	Preferred	Alternative	Duration
Outpatient			
2 - < 5 y/o	**Presumed bacterial pneumonia**		
	Amoxicillin (90 mg/kg/day, in 2–3 doses) Amoxicillin/clavulanate	Cefaclor[b] Cefixime[c]	5–10 days
	Presumed atypical pneumonia		
	Azithromycin	Clarithromycin Erythromycin	Azithromycin 3–5 days Clarithromycin 7–14 days
5–17 years	**Presumed bacterial pneumonia**		
	Amoxicillin (90 mg/kg/day, in 2–3 doses, max 4 g/day)	Cefaclor[b] Cefixime[c] Amoxicillin/clavulanate	5–10 days
	Presumed atypical pneumonia[d]		
	Azithromycin	Clarithromycin Doxycycline[e] Tetracycline[e]	

[a] Refer to Table 13 for the recommended dose of antibiotics in children
[b] Or other oral second-generation cephalosporins
[c] Or other oral third-generation cephalosporins
[d] For children with presumed bacterial CAP who do not have clinical, laboratory, or radiographic evidence that distinguishes bacterial pneumonia from atypical pneumonia, a macrolide can be added to a β-lactam antibiotic for empiric therapy
[e] For children older than eight years of age.

Table 11 Empiric therapy for inpatient treatment of community-acquired pneumonia in children.[a]

Age	Preferred	Alternative	Duration
Inpatient			
2–59 months	**Presumed bacterial pneumonia**		
	Penicillin Ampicillin Ampicillin/sulbactam Amoxicillin/clavulanate Cefuroxime	Ceftriaxone[b] Vancomycin[c]	7–10 days
	Presumed atypical pneumonia		
	Azithromycin	Clarithromycin (B, II) Erythromycin (B, II)	Azithromycin 3–5 days Clarithromycin 7–14 days Erythromycin 7–14 days
6–17 years	**Presumed bacterial pneumonia**		10 days
	Penicillin Ampicillin	Ampicillin/sulbactam Amoxicillin/clavulanate Cefuroxime Ceftriaxone[b]	
	Presumed atypical pneumonia		
	Azithromycin[d]	Clarithromycin Doxycycline[e] Tetracycline[e]	Azithromycin 3–5 days Clarithromycin 7–14 days Erythromycin 7–14 days Doxycycline 7–14 days Tetracycline 10 days

[a] Refer to Table 13 for the recommended dose of antibiotics in children
[b] Or other intravenous third-generation cephalosporins except ceftazidime
[c] Vancomycin may be added if community-acquired methicillin-resistant *S. aureus* infection is suspected
[d] Empiric combination therapy with macrolide, in addition to a β-lactam antibiotic, is recommended for the hospitalized children with ages older than 6 years for whom *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are a significant consideration
[e] For children older than eight years of age.

Table 12 Target therapy for community-acquired pneumonia in children.[a]

Pathogens	Preferred	Alternative	Duration[b]
Streptococcus pneumoniae			7–10 days
penicillin MIC			
≤2 μg/mL	Penicillin G Ampicillin Amoxicillin	Ceftriaxone[c]	
≥4 μg/mL	Cefotaxime Ceftriaxone	Vancomycin Linezolid Levofloxacin[d]	
Staphylococcus aureus			
methicillin-susceptible	Oxacillin Cefazolin		≥10–14 days[e]
methicillin-resistant	Vancomycin Teicoplanin Linezolid[f]		
Group A *Streptococcus*	Penicillin G Ampicillin	Ceftriaxone[c] Clindamycin Vancomycin	7–10 days
Haemophilus influenzae			
typeable or nontypeable			
ß-lactamase (-)	Ampicillin Amoxicillin		7–10 days
ß-lactamase (+)	Amoxicillin/clavulanate Ampicillin/sulbactam Cefuroxime	Ceftriaxone[c] Ciprofloxacin[d] Levofloxacin[d]	
Moraxella catarrhalis	Amoxicillin/clavulanate Ampicillin/sulbactam	Ceftriaxone[c]	7–10 days
Mycoplasma pneumoniae	Azithromycin Clarithromycin Erythromcyin	Doxycycline[g] Levofloxacin[d]	7–14 days[h] 3–7 days[i]
Chlamydophila pneumoniae	Azithromycin Clarithromycin Erythromcyin	Doxycycline[g] Levofloxacin[d]	7–14 days[h] 3–7 days[i]

[a] Refer to Table 13 for the recommended dose of antibiotics in children
[b] Duration of antibiotic therapy may be prolonged in those with complicating pneumonia, e.g. bacteremia, empyema, necrotizing pneumonia or lung abscess
[c] Or other intravenous third-generation cephalosporins except ceftazidime
[d] Physician must weight risks and benefits of fluoroquinolones use; growth maturity should also be considered
[e] Treatment duration of *Staphylococcus aureus* pneumonia depends on the clinical severity and complication
[f] Please consult infectious disease specialist for linezolid use
[g] Doxycycline used in children age under 7 years old may lead to dental discoloration. Use with caution
[h] Erythromycin treatment duration
[i] New macrolide, i.e. azithromycin and clarithromycin treatment duration.

distress also require hospitalization. Children with psychosocial concerns, such as poor compliance of therapy or lack of reliable and appropriate care may also warrant admission.[148]

A "toxic appearance" is a clinical status, which may be difficult to define clearly and often relies on clinical experience. It includes but is not limited to pale or cyanotic skin color, lethargy, inconsolable irritability, altered consciousness or cognitive dysfunction, persistently abnormal breathing or heart rate, and prolonged capillary refilling time (Table 8). Children presenting with toxic appearance are at risks of imminent decompensation, which consequently is universally considered as an indication for inpatient care.[148]

Empirical antimicrobial therapy

Outpatient treatment

In otherwise healthy and immunized children with non-severe CAP suspected to be of bacterial origin, amoxicillin is recommended as first-choice, oral antibiotic therapy because of its efficacy against the majority of pathogens causing CAP (Table 10).[149,143,150–153] High-dose amoxicillin (90 mg/kg/day divided into 2–3 doses) is preferable in consideration of the resistance in pneumococci.[149,154,155] Alternative antibiotics include amoxicillin/clavulanate and second-generation cephalosporins. Levofloxacin, moxifloxacin or linezolid can be considered in children with risks of serious penicillin allergy.[149,143,156,157]

Table 13 Dose of antibiotics in children.

Antibiotics	Dose and frequency	Maximum dose
Amoxicillin	90 mg/kg/day PO divided q8-12 h	4000 mg/day
Ampicillin	150—400 mg/kg/day IV divided q6h	12,000 mg/day[a]
Amoxicillin/clavulanate	Amoxicillin 90 mg/kg/day PO divided q6-8 h	4000 mg/day
Amoxicillin/clavulanate	Amoxicillin 100—200 mg/kg/day IV divided q6-8 h	4000 mg/day
Ampicillin/sulbactam	Ampicillin 150—400 mg/kg/day IV divided q6-8 h	2000 mg/dose
Azithromycin	10 mg/kg/day PO qd on day 1—3 or	500 mg/day on day 1—3 or
	10 mg/kg/day PO qd on day 1 then 5 mg/kg/day qd on day 2—5	500 mg/day on day 1 then 250 mg/day on day 2—5
Cefaclor	20—40 mg/kg/day PO divided q8h	1000 mg/day
Cefazolin	100—150 mg/kg/day IV divided q8h	2000 mg/dose
Cefixime	8 mg/kg/day PO divided q12 h-qd	400 mg/day
Cefotaxime	150—200 mg/kg/day IV divided q6-8 h	2000 mg/dose
Ceftibuten	9 mg/kg/day PO qd	400 mg/day
Ceftriaxone	50—100 mg/kg/day IV divided q12 h-qd	2000 mg/day[b]
Cefuroxime	100—200 mg/kg/day IV divided q6-8 h	1500 mg/dose
Cefuroxime axetil	20 50 mg/kg/day PO divided q12 h	500 mg/dose
Cephalexin	75—100 mg/kg/day PO divided q6-8 h	4000 mg/day
Clarithromycin	15 mg/kg/day PO divided q12 h	500 mg/dose
Clindamycin	30—40 mg/kg/day PO divided q8h	1800 mg/day
Clindamycin	40 mg/kg/day IV divided q6-8 h	2700 mg/day
Dicloxacillin	50—100 mg/kg/day PO divided q6h	500 mg/dose
Doxycycline	4.4 mg/kg/day PO divided q12 h-qd on day 1, then	200 mg/day
	2.2—4.4[c] mg/kg/day PO divided q12 h-qd	
Erythromycin	40 mg/kg/day PO divided q6h	4000 mg/day
Levofloxacin	6 months - 5 years: 8—10 mg/kg/dose PO q12 h	750 mg/day
	≥5 years: 8—10 mg/kg/dose PO qd	750 mg/day
Levofloxacin	6 months-5 years: 8—10 mg/kg/dose IV q12 h	750 mg/day
	≥5 years: 8—10 mg/kg/dose IV qd	750 mg/day
Linezolid	<12 years: 30 mg/kg/day IV divided q8h or PO divided into 3 doses	600 mg/dose
	≥12 years: 20 mg/kg/day IV divided q12 h or PO divided into 2 doses	
Oxacillin	150—200 mg/kg/day IV divided q6-8 h	12,000 mg/day
Penicillin G	200,000—400,000 unit/kg/day IV divided q4-6 h	24,000,000 units/day
Teicoplanin	Loading dose: 10 mg/kg IV q12 h for 3 doses, then	Maximal loading dose:
	maintenance dose: 6—10 mg/kg IV qd	400 mg/dose
Tetracycline	25—50 mg/kg/day PO divided q6—12 h	500 mg/dose
Vancomycin	40—60 mg/kg/day IV divided q6—8 h	4000 mg/day

[a] *S. pneumoniae* (MIC for penicillin ≤2 μg/mL), 150—200 mg/kg/day divided every 6 h; *S. pneumoniae* (MIC for penicillin ≥4 μg/mL), 300—400 mg/kg/day divided every 6 h

[b] Higher maximum daily doses up to 4000 mg/day have been recommended for HIV-exposed/HIV-positive patients

[c] 4.4 mg/kg/day for severe infection.

In healthy, immunized, school-aged (≥5 years) children, atypical bacterial pathogens should also be considered. If an atypical bacterial pathogen is suspected clinically, a macrolide is recommended instead.[149,143,156] The role of β-lactam/macrolide combination therapy of pediatric CAP in the outpatient setting is inconclusive so far. A retrospective study in school-aged children receiving outpatient treatment for pneumonia, found a lower treatment failure rate using combination therapy, however, this benefit was not observed in children under six years of age.[158] A recent prospective, observational study of non-severe CAP in children aged 2—59 months treated with amoxicillin, found that there was no significant differences in treatment failure rate on evaluation at day 2 and 5, in children with and without serological diagnosis of acute atypical infection (including *M. pneumoniae*, *C. pneumoniae* and *C. trachomatis*), with a low overall rate of amoxicillin substitution (3.4%). The authors suggest that an empirical non-β-lactam antibiotic was not necessary for children aged 2—59 months with a non-severe CAP as a first-line therapy.[159] We therefore recommend that in non-severe CAP in the outpatient setting, when clinical differentiation between bacterial and atypical pneumonia is doubtful, empirical β-lactam/macrolide combination therapy may benefit children aged 6—18 years. This benefit was not demonstrated in the preschool population.

With regard to treatment duration, although a 10-day treatment course is best studied and known to be effective,

a shorter course may be justified as sufficient. For non-severe pneumonia in the under-fives, a 3-day antibiotic therapy seemed to be as effective as 5 days, based on prospective studies conducted in low-middle income countries.[131,160] However, in these studies, the World Health Organization (WHO) definition for pneumonia was used, in which radiological exams were not required for diagnosis of pneumonia, and consequently children with simply viral infections may also be included. Another prospective study in Israel, where the penicillin resistance was high, suggested that a 5-day course with high dose amoxicillin (80 mg/kg/day) was not inferior to a 10-day course in preschool outpatients with community-acquired alveolar pneumonia, but a 3-day course may be associated with an unacceptable rate of treatment failure.[161] We recommend a treatment duration of 5—10 days for non-severe, bacterial pneumonia in the outpatient setting.

Inpatient treatment

Antimicrobial therapy is not routinely required for preschool-age children with CAP, because viral pathogens are responsible for the great majority of clinical diseases.[162] However, children with suspected bacterial CAP that are serious and warrant hospitalizations should be treated with parenteral antibiotics to provide a reliable drug level in the blood and tissue.

Empirical antimicrobial therapy for inpatients should provide adequate coverage for the bacterial pathogens most likely to cause lower respiratory tract infections based on the local epidemiology (Table 11). In the pre-vaccination era, *S. pneumoniae* was the most common pneumonia pathogen and may lead to serious sequelae without adequate treatment.[61,163,164] A higher dose of penicillin or ampicillin is recommended in the treatment of susceptible or intermediate-susceptible pneumococci. Both penicillin G (400,000 U/kg/day given every 4—6 h) or ampicillin (150—200 mg/kg/day given every 6 h) can be considered as first-choice therapy.

Since the launch of the catch-up immunization program of PCV13 in children aged 2—5 years in 2013 in Taiwan, the incidence of IPD decreased significantly in this age group, from 22.8 cases per 100,000 person-years in 2011—2012 to 11.9 cases per 100,000 person-years in 2013.[165] The catch-up program was extended to children aged 1 year in 2014, and the incidence of IPD among children 1 year of age decreased from 11.4 cases per 100,000 person-years in 2013 to 7.1 cases per 100,000 person-years in 2014.[165] Serotype 19A was the most prevalent serotype for IPD in Taiwanese children aged <5 years in 2009—2014.[166,167] The incidence of serotype 19A IPD also decreased from 12.9 cases per 100,000 person-years in 2011—2012 to 6.0 cases per 100,000 person-years in 2013 after implementation of PCV13 catch-up immunization program.[166] Despite a minor serotype replacement phenomenon with emergence of serotypes not covered by PCV13 (especially serotype 15, 23, and 35) in IPD, the overall incidence of IPD continues to decline. However, if there are concerns about breakthrough IPD caused by serotype 19A[168] or possession of high antimicrobial resistance, ceftriaxone or cefotaxime may be considered as an alternative empirical antibiotics therapy. *In vitro*, both ceftriaxone and cefotaxime are substantially more active against penicillin-resistant strains than penicillin G.[169]

After the introduction of DTaP-Hib-IPV vaccine in the NIP in 2010 in Taiwan, *H. influenzae* type b (Hib) diseases decreased in children.[170] Therefore, Hib is no longer considered a major pathogen in childhood CAP or invasive disease.[61] The exception is in children with chronic lung diseases, in whom nontypeable *H. influenzae* (NTHi) is sometimes responsible for pediatric pneumonia. Because NTHi strains with positive β-lactamase are prevalent in Taiwan, the second-generation cephalosporin (e.g., cefuroxime or cefaclor) or β-lactam plus β-lactamase inhibitor (e.g., ampicillin/sulbactam or amoxicillin/clavulanate) is recommended instead of penicillin G or ampicillin when NTHi is a presumed pathogen.[171]

M. pneumoniae is the second leading bacterial pathogens in childhood CAP in Taiwan.[172] Earlier studies demonstrated that school-aged patients who were hospitalized for CAP and received combination therapy of β-lactam and macrolide had a shorter length of stay and similar rates of readmission compared with those who received β-lactam alone.[173] However, this benefit was not demonstrated in preschool-aged children, and has the disadvantage of higher medical costs.[174] A recent, multicenter, prospective, population-based study of CAP recruiting children with a median age of 27 months (interquartile range 12—69 months) in the United States, found that there was no statistically significant difference in the length of hospital stay between children receiving β-lactam monotherapy and β-lactam plus macrolide combination therapy. In the Taiwan Pediatric Infectious Disease Alliance (TPIDA) project, significantly longer hospitalizations, higher admission rates to the ICU, and more complications were found in children aged under five years with CAP due to *M. pneumoniae*, hospitalized in 9 medical centers across Taiwan.[172] Overall 60.6% received macrolides. We recommend β-lactam and macrolide combination therapy for hospitalized children, especially school-aged, with CAP.

Pathogen-specific therapy

Despite the low yield rate of blood culture among children with CAP,[175] antibiotic treatment should be adjusted accordingly once the pathogen is identified and the results of the drug susceptibility test are available to minimize the emergence of antibiotic resistance (Table 12).[176]

1. *S. pneumoniae*

The 2008 revision of Clinical and Laboratory Standards Institute guidelines changed the penicillin susceptibility MIC breakpoints for *S. pneumoniae* in non-meningitis cases,[177] in which penicillin MIC ≤2 μg/mL was defined as susceptible, whereas 4 μg/mL as intermediate and ≥8 μg/mL as resistant. Application of the new MIC breakpoints on the data from Taiwan's national surveillance system for IPD in all age groups, the penicillin-resistant rate in *S. pneumoniae* strains causing IPD in 2008 was 6.4%, dropping to 1.9% in 2016.[178] There was a trend of increasing drug susceptibility in *S. pneumoniae* after 2012 in other antibiotics commonly used for pneumococcal infection in children,

such as amoxicillin and cefotaxime.[178] The declining antibiotic resistance in *S. pneumoniae* seemed to be associated with the reduction of the highly antibiotic resistant serotype, 19A, after the introduction of PCV13 catch-up program since 2013 in Taiwan. On the other hand, the percentage of IPD isolates resistant to FQ or vancomycin still remained very low throughout these years. Changes in both the bacterial etiology of CAP and the antibiotics susceptibility rates will impact on the optimal choice of antibiotics in the post-PCV era.[66]

2. *H. influenzae* & *M. catarrhalis*

Hib-associated invasive disease among children became rare after universal inoculation of Hib conjugated vaccine in Taiwan. By contrast, the percentage of NTHi infection is increasing. A study found that the susceptibility of amoxicillin against NTHi decreased from 30% to 20% in the past decade in Taiwan, which may be associated with increasing β-lactamase-producing strains.[179] On the other hand, only about 20—25% of the NTHi strains were resistant to amoxicillin/clavulanate. Amoxicillin/clavulanate, instead of amoxicillin, is recommended for treatment of CAP caused by NTHi in children.[179]

Most strains of *M. catarrhalis* produced β-lactamase (97.8%) and were resistant to amoxicillin in Taiwan.[114] Several pharmacokinetic/pharmacodynamics studies suggested that high dose amoxicillin/clavulanate, cefotaxime or ceftriaxone may be adequate to treat *M. catarrhalis* infection.[180]

3. *S. aureus*

S. aureus can cause severe CAP and complications among children, especially in the influenza season. The drugs of choice for community acquired-methicillin resistant *S. aureus* pneumonia are vancomycin, teicoplanin, and linezolid. We recommend linezolid as first-line antibiotic to treat *S. aureus* with vancomycin MIC $\geq$2 μg/mL.

4. *M. pneumoniae*

It is difficult to culture *M. pneumoniae* from respiratory tract specimens. The drug of choice for *M. pneumoniae* pneumonia is a macrolide. However, specific point mutations of 23S rRNA in *M. pneumoniae* express high resistance to macrolides.[181] The prevalence of macrolide-resistant *M. pneumoniae* among children hospitalized for CAP in Taiwan is around 12—23%, which is much lower than other Asian countries such as China, Japan and Korea.[63,64,182,183] Tetracyclines and FQ are alternatives for treatment of macrolide-resistant mycoplasma pneumonia, but their adverse effects in young-aged children group limit the clinical use.[184] Enamel staining in children using tetracyclines is a major concern. However, a recent study demonstrated that short-course doxycycline treatment did not cause enamel staining in children under 8 years old.[185] Clinicians should weigh the possible adverse effects and clinical benefits before starting tetracycline and FQ treatment in children. These alternative antibiotics may also be considered when patients remain febrile or have radiological deterioration on chest x-rays 48—72 h after macrolide treatment.[186]

Time-out and de-escalation

There is no good randomized controlled study to define the optimal duration of antibiotic therapy for CAP in children. Most experts and textbooks recommend that 7—10 days of antibiotic treatment is appropriate for most pediatric CAP without complications.[176,180] However, the treatment duration should be extended if complications develop, including sepsis, metastatic infection, necrotizing pneumonitis, lung abscess or empyema. Surgical intervention should be considered in cases developing abscess or empyema. Pediatric CAP caused by *S. aureus* may require treatment longer than 10—14 days. The appropriate duration of treatment of *S. aureus* pneumonia varied based on clinical severity and complications.[187]

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Appendix A. Supplementary data

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