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The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America

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Evidenced-based guidelines for management of infants and children with community-acquired pneumonia (CAP) were prepared by an expert panel comprising clinicians and investigators representing community pediatrics, public health, and the pediatric specialties of critical care, emergency medicine, hospital medicine, infectious diseases, pulmonology, and surgery. These guidelines are intended for use by primary care and subspecialty providers responsible for the management of otherwise healthy infants and children with CAP in both outpatient and inpatient settings. Site-of-care management, diagnosis, antimicrobial and adjunctive surgical therapy, and prevention are discussed. Areas that warrant future investigations are also highlighted.

EXECUTIVE SUMMARY

Guidelines for the management of community-acquired pneumonia (CAP) in adults have been demonstrated to decrease morbidity and mortality rates [1, 2]. These guidelines were created to assist the clinician in the care of a child with CAP. They do not represent the only approach to diagnosis and therapy; there is considerable variation among children in the clinical course of pediatric CAP, even with infection caused by the same pathogen. The goal of these guidelines is to decrease morbidity and mortality rates for CAP in children by presenting recommendations for clinical management that can be applied in individual cases if deemed appropriate by the treating clinician.

This document is designed to provide guidance in the care of otherwise healthy infants and children and addresses practical questions of diagnosis and management of CAP evaluated in outpatient (offices, urgent care clinics, emergency departments) or inpatient settings in the United States. Management of neonates and young infants through the first 3 months, immunocompromised

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children, children receiving home mechanical ventilation, and children with chronic conditions or underlying lung disease, such as cystic fibrosis, are beyond the scope of these guidelines and are not discussed.

Summarized below are the recommendations made in the new 2011 pediatric CAP guidelines. The panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines, which included a systematic weighting of the quality of the evidence and the grade of the recommendation [3] (Table 1). A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guidelines.

SITE-OF-CARE MANAGEMENT DECISIONS

I. When Does a Child or Infant With CAP Require Hospitalization?

Recommendations

1. Children and infants who have moderate to severe CAP, as defined by several factors, including respiratory distress and hypoxemia (sustained saturation of peripheral oxygen [SpO_2], <90 % at sea level) (Table 3) should be hospitalized for management, including skilled pediatric nursing care. *(strong recommendation; high-quality evidence)*
2. Infants less than 3–6 months of age with suspected bacterial CAP are likely to benefit from hospitalization. *(strong recommendation; low-quality evidence)*
3. Children and infants with suspected or documented CAP caused by a pathogen with increased virulence, such as community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) should be hospitalized. *(strong recommendation; low-quality evidence)*
4. 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 should be hospitalized. *(strong recommendation; low-quality evidence)*

II. When Should a Child With CAP Be Admitted to an Intensive Care Unit (ICU) or a Unit With Continuous Cardiorespiratory Monitoring?

Recommendations

5. A child should be admitted to an ICU if the child requires invasive ventilation via a nonpermanent artificial airway (eg, endotracheal tube). *(strong recommendation; high-quality evidence)*
6. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child acutely requires use of noninvasive positive pressure ventilation (eg, continuous positive airway pressure or bilevel positive airway pressure). *(strong recommendation; very low-quality evidence)*
7. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child has impending respiratory failure. *(strong recommendation; moderate-quality evidence)*
8. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child has sustained tachycardia, inadequate blood pressure, or need for pharmacologic support of blood pressure or perfusion. *(strong recommendation; moderate-quality evidence)*
9. A child should be admitted to an ICU if the pulse oximetry measurement is <92% on inspired oxygen of ≥0.50. *(strong recommendation; low-quality evidence)*
10. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child has altered mental status, whether due to hypercarbia or hypoxemia as a result of pneumonia. *(strong recommendation; low-quality evidence)*
11. 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. *(strong recommendation; low-quality evidence)*

DIAGNOSTIC TESTING FOR PEDIATRIC CAP

III. What Diagnostic Laboratory and Imaging Tests Should Be Used in a Child With Suspected CAP in an Outpatient or Inpatient Setting?

Recommendations

Microbiologic Testing

Blood Cultures: Outpatient

12. Blood cultures should not be routinely performed in nontoxic, fully immunized children with CAP managed in the outpatient setting. *(strong recommendation; moderate-quality evidence)*
13. Blood cultures should be obtained in children who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration after initiation of antibiotic therapy *(strong recommendation; moderate-quality evidence).*

Blood Cultures: Inpatient

14. Blood cultures should be obtained in children requiring hospitalization for presumed bacterial CAP that is moderate to severe, particularly those with complicated pneumonia. *(strong recommendation; low-quality evidence)*
15. 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. *(weak recommendation; low-quality evidence)*

Table 1. Strength of Recommendations and Quality of Evidence

Strength of recommendation and quality of evidence	Clarity of balance between desirable and undesirable effects	Methodologic quality of supporting evidence (examples)	Implications
Strong recommendation			
High-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs[a] or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances; further research is unlikely to change our confidence in the estimate of effect.
Moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for ≥1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher quality evidence becomes available; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality evidence (rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for ≥1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher quality evidence becomes available; any estimate of effect for ≥1 critical outcome is very uncertain.
Weak recommendation			
High-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values; further research is unlikely to change our confidence in the estimate of effect.
Moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches are likely to be better for some patients under some circumstances; further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for ≥1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality evidence	Major uncertainty in estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects may be closely balanced	Evidence for ≥1 critical outcome from unsystematic clinical observations or 2very indirect evidence	Other alternatives may be equally reasonable; any estimate of effect, for at ≥1 critical outcome, is very uncertain.

[a] RCTs, randomized controlled trials.

Table 2. Complications Associated With Community-Acquired Pneumonia

Pulmonary
Pleural effusion or empyema
Pneumothorax
Lung abscess
Bronchopleural fistula
Necrotizing pneumonia
Acute respiratory failure
Metastatic
Meningitis
Central nervous system abscess
Pericarditis
Endocarditis
Osteomyelitis
Septic arthritis
Systemic
Systemic inflammatory response syndrome or sepsis
Hemolytic uremic syndrome

Follow-up Blood Cultures

16. Repeated blood cultures in children with clear clinical improvement are not necessary to document resolution of pneumococcal bacteremia. *(weak recommendation; low-quality evidence)*

17. Repeated blood cultures to document resolution of bacteremia should be obtained in children with bacteremia caused by *S. aureus*, regardless of clinical status. *(strong recommendation; low-quality evidence)*

Sputum Gram Stain and Culture

18. Sputum samples for culture and Gram stain should be obtained in hospitalized children who can produce sputum. *(weak recommendation; low-quality evidence)*

Table 3. Criteria for Respiratory Distress in Children With Pneumonia

Signs of Respiratory Distress
1. Tachypnea, respiratory rate, breaths/min[a]
Age 0–2 months: >60
Age 2–12 months: >50
Age 1–5 Years: >40
Age >5 Years: >20
2. Dyspnea
3. Retractions (suprasternal, intercostals, or subcostal)
4. Grunting
5. Nasal flaring
6. Apnea
7. Altered mental status
8. Pulse oximetry measurement <90% on room air

[a] Adapted from World Health Organization criteria.

Urinary Antigen Detection Tests

19. Urinary antigen detection tests are not recommended for the diagnosis of pneumococcal pneumonia in children; false-positive tests are common. *(strong recommendation; high-quality evidence)*

Testing For Viral Pathogens

20. Sensitive and specific tests for the rapid diagnosis of influenza virus and other respiratory viruses should be used in the evaluation of children with CAP. A positive influenza test may decrease both the need for additional diagnostic studies and antibiotic use, while guiding appropriate use of antiviral agents in both outpatient and inpatient settings. *(strong recommendation; high-quality evidence)*

21. Antibacterial therapy is not necessary for children, either outpatients or inpatients, with a positive test for influenza virus in the absence of clinical, laboratory, or radiographic findings that suggest bacterial coinfection. *(strong recommendation; high-quality evidence)*.

22. 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 coinfection. *(weak recommendation; low-quality evidence)*

Testing for Atypical Bacteria

23. Children with signs and symptoms suspicious for *Mycoplasma pneumoniae* should be tested to help guide antibiotic selection. *(weak recommendation; moderate-quality evidence)*

24. Diagnostic testing for *Chlamydophila pneumoniae* is not recommended as reliable and readily available diagnostic tests do not currently exist. *(strong recommendation; high-quality evidence)*

Ancillary Diagnostic Testing

Complete Blood Cell Count

25. Routine measurement of the complete blood cell count is not necessary in all children with suspected CAP managed in the outpatient setting, but in those with more serious disease it may provide useful information for clinical management in the context of the clinical examination and other laboratory and imaging studies. *(weak recommendation; low-quality evidence)*

26. A complete blood cell count should be obtained for patients with severe pneumonia, to be interpreted in the context of the clinical examination and other laboratory and imaging studies. *(weak recommendation; low-quality evidence)*

Acute-Phase Reactants

27. Acute-phase reactants, 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. *(strong recommendation; high-quality evidence)*

28. Acute-phase reactants need not be routinely measured in fully immunized children with CAP who are managed as outpatients, although for more serious disease, acute-phase reactants may provide useful information for clinical management. *(strong recommendation; low-quality evidence)*

29. In patients with more serious disease, such as those requiring hospitalization or those with pneumonia-associated complications, acute-phase reactants may be used in conjunction with clinical findings to assess response to therapy. *(weak recommendation; low-quality evidence)*

Pulse Oximetry

30. Pulse oximetry should be performed in all children with pneumonia and suspected hypoxemia. The presence of hypoxemia should guide decisions regarding site of care and further diagnostic testing. *(strong recommendation; moderate-quality evidence)*

Chest Radiography

Initial Chest Radiographs: Outpatient

31. Routine chest radiographs are not necessary for the confirmation of suspected CAP in patients well enough to be treated in the outpatient setting (after evaluation in the office, clinic, or emergency department setting). *(strong recommendation; high-quality evidence)*

32. Chest radiographs, posteroanterior and lateral, should be obtained in patients with suspected or documented hypoxemia or significant respiratory distress (Table 3) and in those with failed initial antibiotic therapy to verify the presence or absence of complications of pneumonia, including parapneumonic effusions, necrotizing pneumonia, and pneumothorax. *(strong recommendation; moderate-quality evidence)*

Initial Chest Radiographs: Inpatient

33. Chest radiographs (posteroanterior and lateral) should be obtained in all patients hospitalized for management of CAP to document the presence, size, and character of parenchymal infiltrates and identify complications of pneumonia that may lead to interventions beyond antimicrobial agents and supportive medical therapy. *(strong recommendation; moderate-quality evidence)*

Follow-up Chest Radiograph

34. Repeated chest radiographs are not routinely required in children who recover uneventfully from an episode of CAP. *(strong recommendation; moderate-quality evidence)*

Table 4. Criteria for CAP Severity of Illness in Children with Community-Acquired Pneumonia

Criteria
Major criteria
Invasive mechanical ventilation
Fluid refractory shock
Acute need for NIPPV
Hypoxemia requiring FiO_2 greater than inspired concentration or flow feasible in general care area
Minor criteria
Respiratory rate higher than WHO classification for age
Apnea
Increased work of breathing (eg, retractions, dyspnea, nasal flaring, grunting)
PaO2/FiO2 ratio <250
Multilobar infiltrates
PEWS score >6
Altered mental status
Hypotension
Presence of effusion
Comorbid conditions (eg, HgbSS, immunosuppression, immunodeficiency)
Unexplained metabolic acidosis

Modified from Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults [27, table 4]. Clinician should consider care in an intensive care unit or a unit with continuous cardiorespiratory monitoring for the child having ≥1 major or ≥2 minor criteria.

Abbreviations: FiO_2, fraction of inspired oxygen; HgbSS, Hemoglobin SS disease; NIPPV, noninvasive positive pressure ventilation; PaO2, arterial oxygen pressure; PEWS, Pediatric Early Warning Score [70].

35. Repeated chest radiographs should be obtained in children who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration within 48–72 hours after initiation of antibiotic therapy. *(strong recommendation; moderate-quality evidence)*

36. Routine daily chest radiography is not recommended in children with pneumonia complicated by parapneumonic effusion after chest tube placement or after video-assisted thoracoscopic surgery (VATS), if they remain clinically stable. *(strong recommendation; low-quality evidence)*

37. Follow-up chest radiographs should be obtained in patients with complicated pneumonia with worsening respiratory distress or clinical instability, or in those with persistent fever that is not responding to therapy over 48-72 hours. *(strong recommendation; low-quality evidence)*

38. 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. *(strong recommendation; moderate-quality evidence)*

IV. What Additional Diagnostic Tests Should Be Used in a Child With Severe or Life-Threatening CAP?

Recommendations

39. The clinician should obtain tracheal aspirates for Gram stain and culture, as well as clinically and epidemiologically guided testing for viral pathogens, including influenza virus, at the time of initial endotracheal tube placement in children requiring mechanical ventilation. *(strong recommendation; low-quality evidence)*

40. Bronchoscopic or blind protected specimen brush sampling, bronchoalveolar lavage (BAL), percutaneous lung aspiration, or open lung biopsy should be reserved for the immunocompetent child with severe CAP if initial diagnostic tests are not positive. *(weak recommendation; low-quality evidence)*

ANTI-INFECTIVE TREATMENT

V. Which Anti-Infective Therapy Should Be Provided to a Child With Suspected CAP in Both Outpatient and Inpatient Settings?

Recommendations

Outpatients

41. Antimicrobial therapy is not routinely required for preschool-aged children with CAP, because viral pathogens are responsible for the great majority of clinical disease. *(strong recommendation; high-quality evidence)*

42. Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae,* the most prominent invasive bacterial pathogen. Table 5 lists preferred agents and alternative agents for children allergic to amoxicillin *(strong recommendation; moderate-quality evidence)*

43. Amoxicillin should be used as first-line therapy for previously healthy appropriately immunized school-aged children and adolescents with mild to moderate CAP for *S. pneumoniae*, the most prominent invasive bacterial pathogen. Atypical bacterial pathogens (eg, *M. pneumoniae*), and less common lower respiratory tract bacterial pathogens, as discussed in the Evidence Summary, should also be considered in management decisions. *(strong recommendation; moderate-quality evidence)*

44. Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens. Laboratory testing for *M. pneumoniae* should be performed if available in a clinically relevant time frame. Table 5 lists preferred and alternative agents for atypical pathogens. *(weak recommendation; moderate-quality evidence)*

45. Influenza antiviral therapy (Table 6) should be administered as soon as possible to children with moderate to severe CAP consistent with influenza virus infection during widespread local circulation of influenza viruses, particularly for those with clinically worsening disease documented at the time of an outpatient visit. Because early antiviral treatment has been shown to provide maximal benefit, treatment should not be delayed until confirmation of positive influenza test results. Negative results of influenza diagnostic tests, especially rapid antigen tests, do not conclusively exclude influenza disease. Treatment after 48 hours of symptomatic infection may still provide clinical benefit to those with more severe disease. *(strong recommendation; moderate-quality evidence)*

Inpatients

46. Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae.* Other antimicrobial agents for empiric therapy are provided in Table 7. *(strong recommendation; moderate-quality evidence)*

47. Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema (Table 7). Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. *(weak recommendation; moderate-quality evidence)*

48. Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations; diagnostic testing should be performed if available in a clinically relevant time frame (Table 7). *(weak recommendation; moderate-quality evidence)*

49. Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *S. aureus* (Table 7). *(strong recommendation; low-quality evidence)*

Table 5. Selection of Antimicrobial Therapy for Specific Pathogens

Pathogen	Parenteral therapy	Oral therapy (step-down therapy or mild infection)
Streptococcus pneumoniae with MICs for penicillin ≤2.0 μg/mL	Preferred: ampicillin (150–200 mg/kg/day every 6 hours) or penicillin (200 000–250 000 U/kg/day every 4–6 h); Alternatives: ceftriaxone (50–100 mg/kg/day every 12–24 hours) (preferred for parenteral outpatient therapy) or cefotaxime (150 mg/kg/day every 8 hours); may also be effective: clindamycin (40 mg/kg/day every 6–8 hours) or vancomycin (40–60 mg/kg/day every 6–8 hours)	Preferred: amoxicillin (90 mg/kg/day in 2 doses or 45 mg/kg/day in 3 doses); Alternatives: second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil); oral levofloxacin, if susceptible (16–20 mg/kg/day in 2 doses for children 6 months to 5 years old and 8–10 mg/kg/day once daily for children 5 to 16 years old; maximum daily dose, 750 mg) or oral linezolid (30 mg/kg/day in 3 doses for children <12 years old and 20 mg/kg/day in 2 doses for children ≥12 years old)
S. pneumoniae resistant to penicillin, with MICs ≥4.0 μg/mL	Preferred: ceftriaxone (100 mg/kg/day every 12–24 hours); Alternatives: ampicillin (300–400 mg/kg/day every 6 hours), levofloxacin (16–20 mg/kg/day every 12 hours for children 6 months to 5 years old and 8–10 mg/kg/day once daily for children 5–16 years old; maximum daily dose, 750 mg), or linezolid (30 mg/kg/day every 8 hours for children <12 years old and 20 mg/kg/day every 12 hours for children ≥12 years old); may also be effective: clindamycin[a] (40 mg/kg/day every 6–8 hours) or vancomycin (40–60 mg/kg/day every 6–8 hours)	Preferred: oral levofloxacin (16–20 mg/kg/day in 2 doses for children 6 months to 5 years and 8–10 mg/kg/day once daily for children 5–16 years, maximum daily dose, 750 mg), if susceptible, or oral linezolid (30 mg/kg/day in 3 doses for children <12 years and 20 mg/kg/day in 2 doses for children ≥12 years); Alternative: oral clindamycin[a] (30–40 mg/kg/day in 3 doses)
Group A *Streptococcus*	Preferred: intravenous penicillin (100 000–250 000 U/kg/day every 4–6 hours) or ampicillin (200 mg/kg/day every 6 hours); Alternatives: ceftriaxone (50–100 mg/kg/day every 12–24 hours) or cefotaxime (150 mg/kg/day every 8 hours); may also be effective: clindamycin, if susceptible (40 mg/kg/day every 6–8 hours) or vancomycin[b] (40–60 mg/kg/day every 6–8 hours)	Preferred: amoxicillin (50–75 mg/kg/day in 2 doses), or penicillin V (50–75 mg/kg/day in 3 or 4 doses); Alternative: oral clindamycin[a] (40 mg/kg/day in 3 doses)
Stapyhylococcus aureus, methicillin susceptible (combination therapy not well studied)	Preferred: cefazolin (150 mg/kg/day every 8 hours) or semisynthetic penicillin, eg oxacillin (150–200 mg/kg/day every 6–8 hours); Alternatives: clindamycin[a] (40 mg/kg/day every 6–8 hours) or >vancomycin (40–60 mg/kg/day every 6–8 hours)	Preferred: oral cephalexin (75–100 mg/kg/day in 3 or 4 doses); Alternative: oral clindamycin[a] (30–40 mg/kg/day in 3 or 4 doses)
S. aureus, methicillin resistant, susceptible to clindamycin (combination therapy not well-studied)	Preferred: vancomycin (40–60 mg/kg/day every 6–8 hours or dosing to achieve an AUC/MIC ratio of >400) or clindamycin (40 mg/kg/day every 6–8 hours); Alternatives: linezolid (30 mg/kg/day every 8 hours for children <12 years old and 20 mg/kg/day every 12 hours for children ≥12 years old)	Preferred: oral clindamycin (30–40 mg/kg/day in 3 or 4 doses); Alternatives: oral linezolid (30 mg/kg/day in 3 doses for children <12 years and 20 mg/kg/day in 2 doses for children ≥12 years)
S. aureus, methicillin resistant, resistant to clindamycin (combination therapy not well studied)	Preferred: vancomycin (40–60 mg/kg/day every 6-8 hours or dosing to achieve an AUC/MIC ratio of >400); Alternatives: linezolid (30 mg/kg/day every 8 hours for children <12 years old and 20 mg/kg/day every 12 hours for children ≥12 years old)	Preferred: oral linezolid (30 mg/kg/day in 3 doses for children <12 years and 20 mg/kg/day in 2 doses for children ≥12 years old); Alternatives: none; entire treatment course with parenteral therapy may be required

Table 5. (*Continued*)

Pathogen	Parenteral therapy	Oral therapy (step-down therapy or mild infection)
Haemophilus influenza, typeable (A-F) or nontypeable	Preferred: intravenous ampicillin (150-200 mg/kg/day every 6 hours) if β-lactamase negative, ceftriaxone (50–100 mg/kg/day every 12-24 hours) if β-lactamase producing, or cefotaxime (150 mg/kg/day every 8 hours); Alternatives: intravenous ciprofloxacin (30 mg/kg/day every 12 hours) or intravenous levofloxacin (16-20 mg/kg/day every 12 hours for children 6 months to 5 years old and 8-10 mg/kg/day once daily for children 5 to 16 years old; maximum daily dose, 750 mg)	Preferred: amoxicillin (75-100 mg/kg/day in 3 doses) if β-lactamase negative) or amoxicillin clavulanate (amoxicillin component, 45 mg/kg/day in 3 doses or 90 mg/kg/day in 2 doses) if β-lactamase producing; Alternatives: cefdinir, cefixime, cefpodoxime, or ceftibuten
Mycoplasma pneumoniae	Preferred: intravenous azithromycin (10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); Alternatives: intravenous erythromycin lactobionate (20 mg/kg/day every 6 hours) or levofloxacin (16-20 mg/kg/day every 12 hours; maximum daily dose, 750 mg)	Preferred: azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5); Alternatives: clarithromycin (15 mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 years old, doxycycline (2–4 mg/kg/day in 2 doses; for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)
Chlamydia trachomatis or *Chlamydophila pneumoniae*	Preferred: intravenous azithromycin (10 mg/kg on days 1 and 2 of therapy; transition to oral therapy if possible); Alternatives: intravenous erythromycin lactobionate (20 mg/kg/day every 6 hours) or levofloxacin (16-20 mg/kg/day in 2 doses for children 6 months to 5 years old and 8-10 mg/kg/day once daily for children 5 to 16 years old; maximum daily dose, 750 mg)	Preferred: azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily days 2–5); Alternatives: clarithromycin (15 mg/kg/day in 2 doses) or oral erythromycin (40 mg/kg/day in 4 doses); for children >7 years old, doxycycline (2-4 mg/kg/day in 2 doses); for adolescents with skeletal maturity, levofloxacin (500 mg once daily) or moxifloxacin (400 mg once daily)

Doses for oral therapy should not exceed adult doses.

Abbreviations: AUC, area under the time vs. serum concentration curve; MIC, minimum inhibitory concentration.

[a] Clindamycin resistance appears to be increasing in certain geographic areas among *S. pneumoniae* and *S. aureus* infections.

[b] For β-lactam–allergic children.

VI. How Can Resistance to Antimicrobials Be Minimized?

Recommendations

50. Antibiotic exposure selects for antibiotic resistance; therefore, limiting exposure to any antibiotic, whenever possible, is preferred. *(strong recommendation; moderate-quality evidence)*

51. Limiting the spectrum of activity of antimicrobials to that specifically required to treat the identified pathogen is preferred. *(strong recommendation; low-quality evidence)*

52. Using the proper dosage of antimicrobial to be able to achieve a minimal effective concentration at the site of infection is important to decrease the development of resistance. *(strong recommendation; low-quality evidence)*

53. Treatment for the shortest effective duration will minimize exposure of both pathogens and normal microbiota to antimicrobials and minimize the selection for resistance. *(strong recommendation; low-quality evidence)*

VII. What Is the Appropriate Duration of Antimicrobial Therapy for CAP?

Recommendations

54. Treatment courses of 10 days have been best studied, although shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis. *(strong recommendation; moderate-quality evidence)*

55. Infections caused by certain pathogens, notably CA-MRSA, may require longer treatment than those caused by *S. pneumoniae*. *(strong recommendation; moderate-quality evidence)*

VIII. How Should the Clinician Follow the Child With CAP for the Expected Response to Therapy?

Recommendation

56. Children on adequate therapy should demonstrate clinical and laboratory signs of improvement within 48–72 hours. For

Table 6. Influenza Antiviral Therapy

Drug [186187]	Formulation	Dosing recommendations: Treatment: Children	Treatment: Adults	Prophylaxis[a]: Children	Prophylaxis[a]: Adults
Oseltamivir (Tamiflu)	75-mg capsule; 60 mg/5 mL Suspension	≥24 months old: ~4 mg/kg/day in 2 doses, for a 5-day treatment course	150 mg/day in 2 doses for 5 days	≤15 kg: 30 mg/day; >15 to 23 kg: 45 mg/day; >23 to 40 kg: 60 mg/day; >40 kg: 75 mg/day (once daily in each group)	75 mg/day once daily
		≤15 kg: 60 mg/day; >15 to 23 kg: 90 mg/day; >23 to 40 kg: 120 mg/day; >40 kg: 150 mg/day (divided into 2 doses for each group)			
		9–23 months old: 7 mg/kg/day in 2 doses; 0–8 months old: 6 mg/kg/day in 2 doses; premature infants: 2 mg/kg/day in 2 doses		9–23 months old: 3.5 mg/kg once daily; 3–8 months old: 3 mg/kg once daily; not routinely recommended for infants <3 months old owing to limited data in this age group	
Zanamivir (Relenza)	5 mg per inhalation, using a Diskhaler	≥7 years old: 2 inhalations (10 mg total per dose), twice daily for 5 days	2 inhalations (10 mg total per dose), twice daily for 5 days	≥5 years old: 2 inhalations (10 mg total per dose), once daily for 10 days	2 inhalations (10 mg total per dose), once daily for 10 days
Amantadine (Symmetrel)[b]	100-mg tablet; 50 mg/5 mL suspension	1–9 years old: 5–8 mg/kg/day as single daily dose or in 2 doses, not to exceed 150 mg/day; 9–12 years old: 200 mg/day in 2 doses (not studied as single daily dose)	200 mg/day, as single daily dose or in 2 doses	1–9 years old: same as treatment dose; 9–12 years old: same as treatment dose	Same as treatment dose
Rimantadine (Flumadine)[b]	100-mg tablet; 50 mg/5 mL suspension	Not FDA approved for treatment in children, but published data exist on safety and efficacy in children; suspension: 1–9 years old: 6.6 mg/kg/day (maximum 150 mg/kg/day) in 2 doses; ≥10 years old: 200 mg/day, as single daily dose or in 2 doses	200 mg/day, either as a single daily dose, or divided into 2 doses	FDA approved for prophylaxis down to 12 months of age. 1–9 years old: 5 mg/kg/day once daily, not to exceed 150 mg; ≥10 years old: 200 mg/day as single daily dose or in 2 doses	200 mg/day, as single daily dose or in 2 doses

NOTE. Check Centers for Disease Control and Prevention Website (http://www.flu.gov/) for current susceptibility data.

[a] In children for whom prophylaxis is indicated, antiviral drugs should be continued for the duration of known influenza activity in the community because of the potential for repeated and unknown exposures or until immunity can be achieved after immunization.

[b] Amantadine and rimantadine should be used for treatment and prophylaxis only in winter seasons during which a majority of influenza A virus strains isolated are adamantine susceptible; the adamantanes should not be used for primary therapy because of the rapid emergence of resistance. However, for patients requiring adamantane therapy, a treatment course of ~7 days is suggested, or until 24–48 hours after the disappearance of signs and symptoms.

children whose condition deteriorates after admission and initiation of antimicrobial therapy or who show no improvement within 48–72 hours, further investigation should be performed. *(strong recommendation; moderate-quality evidence)*

ADJUNCTIVE SURGICAL AND NON–ANTI-INFECTIVE THERAPY FOR PEDIATRIC CAP

IX. How Should a Parapneumonic Effusion Be Identified?

Recommendation

57. History and physical examination may be suggestive of parapneumonic effusion in children suspected of having CAP, but chest radiography should be used to confirm the presence of pleural fluid. If the chest radiograph is not conclusive, then further imaging with chest ultrasound or computed tomography (CT) is recommended. *(strong recommendation; high-quality evidence)*

X. What Factors Are Important in Determining Whether Drainage of the Parapneumonic Effusion Is Required?

Recommendations

58. The size of the effusion is an important factor that determines management (Table 8, Figure 1). *(strong recommendation; moderate-quality evidence)*

Table 7. Empiric Therapy for Pediatric Community-Acquired Pneumonia (CAP)

Site of care	Empiric therapy		
	Presumed bacterial pneumonia	Presumed atypical pneumonia	Presumed influenza pneumonia[a]
Outpatient			
<5 years old (preschool)	Amoxicillin, oral (90 mg/kg/day in 2 doses[b]) Alternative: oral amoxicillin clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses[b])	Azithromycin oral (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5); Alternatives: oral clarithromycin (15 mg/kg/day in 2 doses for 7-14 days) or oral erythromycin (40 mg/kg/day in 4 doses)	Oseltamivir
≥5 years old	Oral amoxicillin (90 mg/kg/day in 2 doses[b] to a maximum of 4 g/day[c]); for children with presumed bacterial CAP who do not have clinical, laboratory, or radiographic evidence that distinguishes bacterial CAP from atypical CAP, a macrolide can be added to a β-lactam antibiotic for empiric therapy; alternative: oral amoxicillin clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses[b] to a maximum dose of 4000 mg/day, eg, one 2000-mg tablet twice daily[b])	Oral azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5 to a maximum of 500 mg on day 1, followed by 250 mg on days 2–5); alternatives: oral clarithromycin (15 mg/kg/day in 2 doses to a maximum of 1 g/day); erythromycin, doxycycline for children >7 years old	Oseltamivir or zanamivir (for children 7 years and older); alternatives: peramivir, oseltamivir and zanamivir (all intravenous) are under clinical investigation in children; intravenous zanamivir available for compassionate use
Inpatient (all ages)[d]			
Fully immunized with conjugate vaccines for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*; local penicillin resistance in invasive strains of pneumococcus is minimal	Ampicillin or penicillin G; alternatives: ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin (in addition to β-lactam, if diagnosis of atypical pneumonia is in doubt); alternatives: clarithromycin or erythromycin; doxycycline for children >7 years old; levofloxacin for children who have reached growth maturity, or who cannot tolerate macrolides	Oseltamivir or zanamivir (for children ≥7 years old; alternatives: peramivir, oseltamivir and zanamivir (all intravenous) are under clinical investigation in children; intravenous zanamivir available for compassionate use
Not fully immunized for *H, influenzae* type b and *S. pneumoniae*; local penicillin resistance in invasive strains of pneumococcus is significant	Ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA; alternative: levofloxacin; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin (in addition to β-lactam, if diagnosis in doubt); alternatives: clarithromycin or erythromycin; doxycycline for children >7 years old; levofloxacin for children who have reached growth maturity or who cannot tolerate macrolides	As above

For children with drug allergy to recommended therapy, see Evidence Summary for Section V. Anti-Infective Therapy. For children with a history of possible, nonserious allergic reactions to amoxicillin, treatment is not well defined and should be individualized. Options include a trial of amoxicillin under medical observation; a trial of an oral cephalosporin that has substantial activity against *S. pneumoniae*, such as cefpodoxime, cefprozil, or cefuroxime, provided under medical supervision; treatment with levofloxacin; treatment with linezolid; treatment with clindamycin (if susceptible); or treatment with a macrolide (if susceptible). For children with bacteremic pneumococcal pneumonia, particular caution should be exercised in selecting alternatives to amoxicillin, given the potential for secondary sites of infection, including meningitis.

Abbreviation: CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*.

[a] See Table 6 for dosages.

[b] See text for discussion of dosage recommendations based on local susceptibility data. Twice daily dosing of amoxicillin or amoxicillin clavulanate may be effective for pneumococci that are susceptible to penicillin.

[c] Not evaluated prospectively for safety.

[d] See Table 5 for dosages.

Table 8. Factors Associated with Outcomes and Indication for Drainage of Parapneumonic Effusions

Size of effusion	Bacteriology	Risk of poor outcome	Tube drainage with or without fibrinolysis *or* VATS[a]
Small: <10 mm on lateral decubitus radiograph *or* opacifies less than one-fourth of hemithorax	Bacterial culture and Gram stain results unknown or negative	Low	No; sampling of pleural fluid is not routinely required
Moderate: >10 mm rim of fluid but opacifies less than half of the hemithorax	Bacterial culture and/or Gram stain results negative *or* positive (empyema)	Low to moderate	No, if the patient has no respiratory compromise and the pleural fluid is not consistent with empyema (sampling of pleural fluid by simple thoracentesis may help determine presence or absence of empyema and need for a drainage procedure, and sampling with a drainage catheter may provide both diagnostic and therapeutic benefit); Yes, if the patient has respiratory compromise or if pleural fluid is consistent with empyema
Large: opacifies more than half of the hemithorax	Bacterial culture and/or Gram stain results positive (empyema)	High	Yes in most cases

[a] VATS, video-assisted thoracoscopic surgery.

59. The child's degree of respiratory compromise is an important factor that determines management of parapneumonic effusions (Table 8, Figure 1) *(strong recommendation; moderate-quality evidence)*

XI. What Laboratory Testing Should Be Performed on Pleural Fluid?

Recommendation

60. Gram stain and bacterial culture of pleural fluid should be performed whenever a pleural fluid specimen is obtained. *(strong recommendation; high-quality evidence)*

61. Antigen testing or nucleic acid amplification through polymerase chain reaction (PCR) increase the detection of pathogens in pleural fluid and may be useful for management. *(strong recommendation; moderate-quality evidence)*

62. Analysis of pleural fluid parameters, such as pH and levels of glucose, protein, and lactate dehydrogenase, rarely change patient management and are not recommended. *(weak recommendation; very low-quality evidence)*

63. Analysis of the pleural fluid white blood cell (WBC) count, with cell differential analysis, is recommended primarily to help differentiate bacterial from mycobacterial etiologies and from malignancy. *(weak recommendation; moderate-quality evidence)*

XII. What Are the Drainage Options for Parapneumonic Effusions?

Recommendations

64. Small, uncomplicated parapneumonic effusions should not routinely be drained and can be treated with antibiotic therapy alone. *(strong recommendation; moderate-quality evidence)*

65. Moderate parapneumonic effusions associated with respiratory distress, large parapneumonic effusions, or documented purulent effusions should be drained. *(strong recommendation; moderate-quality evidence)*

66. Both chest thoracostomy tube drainage with the addition of fibrinolytic agents and VATS have been demonstrated to be effective methods of treatment. The choice of drainage procedure depends on local expertise. Both of these methods are associated with decreased morbidity compared with chest tube drainage alone. However, in patients with moderate-to-large effusions that are free flowing (no loculations), placement of a chest tube without fibrinolytic agents is a reasonable first option. *(strong recommendation; high-quality evidence)*

XIII. When Should VATS or Open Decortication Be Considered in Patients Who Have Had Chest Tube Drainage, With or Without Fibrinolytic Therapy?

Recommendation

67. VATS should be performed when there is persistence of moderate-large effusions and ongoing respiratory compromise despite ~2–3 days of management with a chest tube and completion of fibrinolytic therapy. Open chest débridement with decortication represents another option for management of these children but is associated with higher morbidity rates. *(strong recommendation; low-quality evidence)*

XIV. When Should a Chest Tube Be Removed Either After Primary Drainage or VATS?

68. A chest tube can be removed in the absence of an intrathoracic air leak and when pleural fluid drainage is

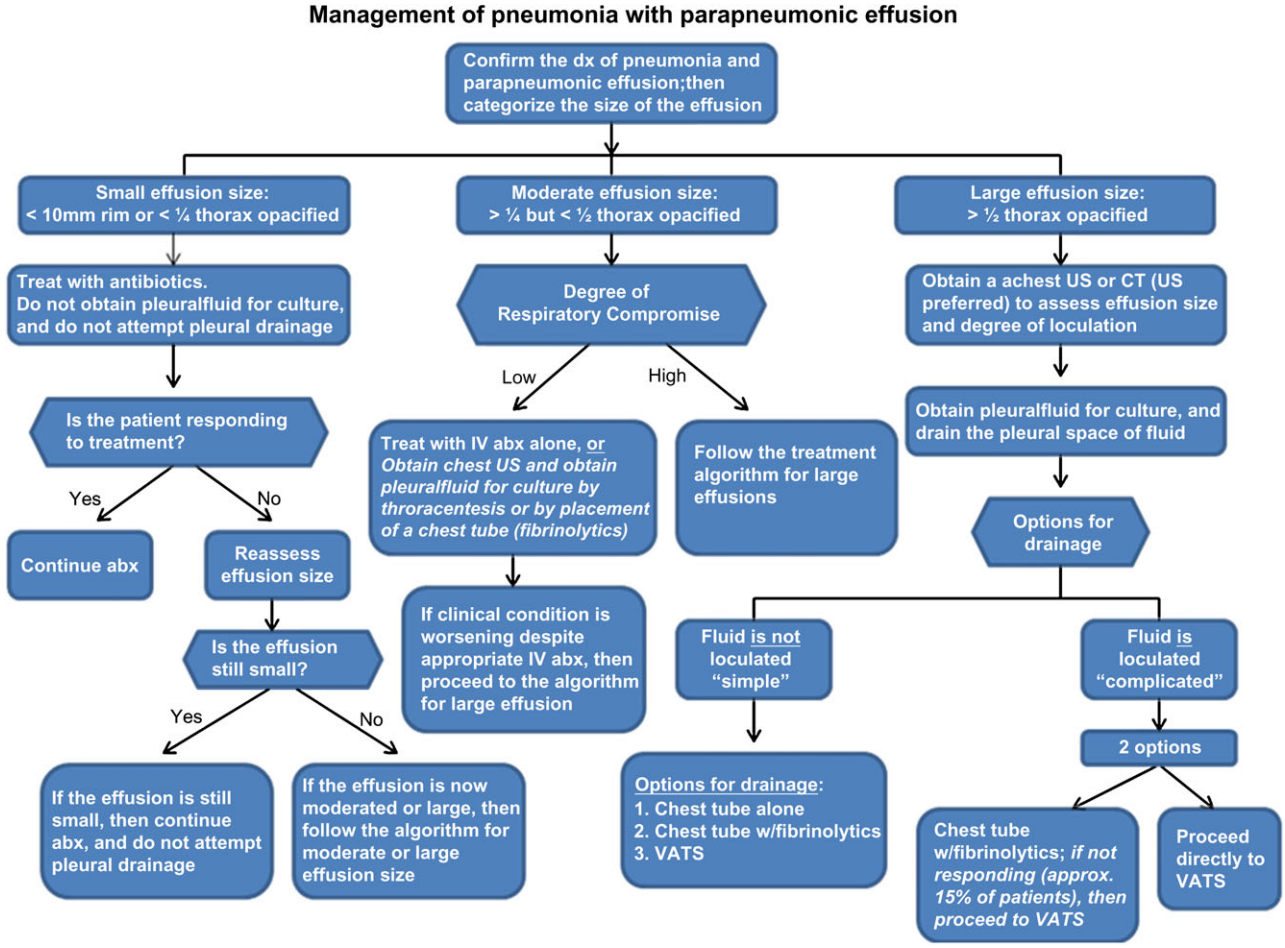

Figure 1. Management of pneumonia with parapneumonic effusion; abx, antibiotics; CT, computed tomography; dx, diagnosis; IV, intravenous; US, ultrasound; VATS, video-assisted thoracoscopic surgery.

<1 mL/kg/24 h, usually calculated over the last 12 hours. *(strong recommendation; very low-quality evidence)*

XV. What Antibiotic Therapy and Duration Is Indicated for the Treatment of Parapneumonic Effusion/Empyema?

Recommendations

69. When the blood or pleural fluid bacterial culture identifies a pathogenic isolate, antibiotic susceptibility should be used to determine the antibiotic regimen. *(strong recommendation; high-quality evidence)*

70. In the case of culture-negative parapneumonic effusions, antibiotic selection should be based on the treatment recommendations for patients hospitalized with CAP (see Evidence Summary for Recommendations 46–49). *(strong recommendation; moderate-quality evidence)*

71. The duration of antibiotic treatment depends on the adequacy of drainage and on the clinical response demonstrated for each patient. In most children, antibiotic treatment for 2–4 weeks is adequate. *(strong recommendation; low-quality evidence)*

MANAGEMENT OF THE CHILD NOT RESPONDING TO TREATMENT

XVI. What Is the Appropriate Management of a Child Who Is Not Responding to Treatment for CAP?

Recommendation

72. Children who are not responding to initial therapy after 48–72 hours should be managed by one or more of the following:

a. Clinical and laboratory assessment of the current severity of illness and anticipated progression in order to determine whether higher levels of care or support are required. *(strong recommendation; low-quality evidence)*

b. Imaging evaluation to assess the extent and progression of the pneumonic or parapneumonic process. *(weak recommendation; low-quality evidence)*

c. Further investigation to identify whether the original pathogen persists, the original pathogen has developed resistance to the agent used, or there is a new secondary infecting agent. *(weak recommendation; low-quality evidence)*

73. A BAL specimen should be obtained for Gram stain and culture for the mechanically ventilated child. *(strong recommendation; moderate-quality evidence)*

74. A percutaneous lung aspirate should be obtained for Gram stain and culture in the persistently and seriously ill child for whom previous investigations have not yielded a microbiologic diagnosis. *(weak recommendation; low-quality evidence)*

75. An open lung biopsy for Gram stain and culture should be obtained in the persistently and critically ill, mechanically ventilated child in whom previous investigations have not yielded a microbiologic diagnosis. *(weak recommendation; low-quality evidence)*

XVII. How Should Nonresponders With Pulmonary Abscess or Necrotizing Pneumonia Be Managed?

Recommendation

76. A pulmonary abscess or necrotizing pneumonia identified in a nonresponding patient can be initially treated with intravenous antibiotics. Well-defined peripheral abscesses without connection to the bronchial tree may be drained under imaging-guided procedures either by aspiration or with a drainage catheter that remains in place, but most abscesses will drain through the bronchial tree and heal without surgical or invasive intervention. *(weak recommendation; very low-quality evidence)*

DISCHARGE CRITERIA

XVIII. When Can a Hospitalized Child With CAP Be Safely Discharged?

Recommendations

77. Patients are eligible for discharge when they have documented overall clinical improvement, including level of activity, appetite, and decreased fever for at least 12–24 hours. *(strong recommendation; very low-quality evidence)*

78. Patients are eligible for discharge when they demonstrate consistent pulse oximetry measurements >90% in room air for at least 12–24 hours. *(strong recommendation; moderate-quality evidence)*

79. Patients are eligible for discharge only if they demonstrate stable and/or baseline mental status. *(strong recommendation; very low-quality evidence)*

80. Patients are not eligible for discharge if they have substantially increased work of breathing or sustained tachypnea or tachycardia *(strong recommendation; high-quality evidence)*

81. 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. *(strong recommendation; low-quality evidence)*

82. For infants or young children requiring outpatient oral antibiotic therapy, clinicians should demonstrate that parents are able to administer and children are able to comply adequately with taking those antibiotics before discharge. *(weak recommendation; very low-quality evidence)*

83. 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. *(strong recommendation; very low-quality evidence)*

84. 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. *(weak recommendation; very low-quality evidence)*

XIX. When Is Parenteral Outpatient Therapy Indicated, In Contrast to Oral Step-Down Therapy?

Recommendations

85. Outpatient parenteral antibiotic therapy should be offered to families of children no longer requiring skilled nursing care in an acute care facility but with a demonstrated need for ongoing parenteral therapy. *(weak recommendation; moderate-quality evidence)*

86. Outpatient parenteral antibiotic therapy should be offered through a skilled pediatric home nursing program or through daily intramuscular injections at an appropriate pediatric outpatient facility. *(weak recommendation; low-quality evidence)*

87. Conversion to oral outpatient step-down therapy when possible, is preferred to parenteral outpatient therapy. *(strong recommendation; low-quality evidence)*

PREVENTION

XX. Can Pediatric CAP Be Prevented?

Recommendations

88. Children should be immunized with vaccines for bacterial pathogens, including *S. pneumoniae*, *Haemophilus influenzae* type b, and pertussis to prevent CAP. *(strong recommendation; high-quality evidence)*

89. All infants ≥6 months of age and all children and adolescents should be immunized annually with vaccines for influenza virus to prevent CAP. *(strong recommendation; high-quality evidence)*

90. Parents and caretakers of infants <6 months of age, including pregnant adolescents, should be immunized with vaccines for influenza virus and pertussis to protect the infants from exposure. *(strong recommendation; weak-quality evidence)*

91. Pneumococcal CAP after influenza virus infection is decreased by immunization against influenza virus. *(strong recommendation; weak-quality evidence)*

92. High-risk infants should be provided immune prophylaxis with respiratory syncytial virus (RSV)–specific monoclonal antibody to decrease the risk of severe pneumonia and hospitalization caused by RSV. *(strong recommendation; high-quality evidence)*

INTRODUCTION

Burden of Disease

Pneumonia is the single greatest cause of death in children worldwide [4]. Each year, >2 million children younger than 5 years die of pneumonia, representing ~20% of all deaths in children within this age group [5]. Although difficult to quantify, it is believed that up to 155 million cases of pneumonia occur in children every year worldwide [5].

In the developed world, the annual incidence of pneumonia is ~3–4 cases per 100 children <5 years old [6, 7]. In the United States, outpatient visit rates for CAP between 1994–1995 and 2002–2003 were defined using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes and reported in the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey and identified rates ranging from 74 to 92 per 1000 children <2 years old to 35–52 per 1000 children 3–6 years old [8]. In 2006, the rate of hospitalization for CAP in children through age 18 years, using data from the Healthcare Cost Utilization Project's Kids' Inpatient Database, also based on ICD-9-CM discharge diagnosis codes, was 201.1 per 100 000 [9]. Infants <1 year old had the highest rate of hospitalization (912.9 per 100 000) whereas children 13–18 years had the lowest rate (62.8 per 100 000) [9]. Data from the Centers for Disease Control and Prevention (CDC) document that in 2006, 525 infants and children <15 years old died in the United States as a result of pneumonia and other lower respiratory tract infections [10]. The reported incidence of pneumonia in children, both pathogen specific and as a general diagnosis, varies across published studies based on definitions used, tests performed, and the goals of the investigators. CAP in children in the United States, the focus of these guidelines, is defined simply as the presence of signs and symptoms of pneumonia in a previously healthy child caused by an infection that has been acquired outside of the hospital [11, 12]. However, pneumonia definitions can also be designed to be very sensitive for epidemiologic considerations (eg, fever and cough) or very specific, as defined by government regulatory agencies for approval of antimicrobials to treat pneumonia (eg, clinical symptoms and signs in combination with radiologic documentation or microbiologic confirmation) [13]. Pneumonia, broadly defined as a lower respiratory tract infection (LRTI), may also be defined in a way that is clinically oriented, to assist practitioners with diagnosis and management.

Etiology

Many pathogens are responsible for CAP in children, most prominently viruses and bacteria [6, 7, 14–18]. Investigators have used a variety of laboratory tests to establish a microbial etiology of CAP. For example, diagnosis of pneumococcal pneumonia has been based on positive cultures of blood, antibody responses, antigen detection, and nucleic acid detection. Each test has different sensitivity, specificity, and positive and negative predictive values that are dependent on the prevalence of the pathogen at the time of testing. Therefore, comparing etiologies of pneumonia between published studies is challenging. More recent investigations have used a variety of sensitive molecular techniques including nucleic acid detection, particularly for viral identification. In many children with LRTI, diagnostic testing may identify 2 or 3 pathogens, including combinations of both viruses and bacteria, making it difficult to determine the significance of any single pathogen [19–21]. Furthermore, unique to pediatrics, the developing immune system and age-related exposures result in infection caused by different bacterial and viral pathogens, requiring that the incidence of CAP and potential pathogens be defined separately for each age group [7].

The advent of polysaccharide-protein conjugate vaccines for *H. influenzae* type b and 7 serotypes of *S. pneumoniae* (7-valent pneumococcal conjugate vaccine [PCV7]) dramatically decreased the incidence of infection, including CAP, caused by these bacteria. Newer vaccines that protect against a greater number of pneumococcal serotypes are in various stages of clinical development, with a newly licensed 13-valent pneumococcal conjugate vaccine (PCV13) available in the United States. Reports of epidemiologic investigations on the etiology of CAP before the widespread use of these vaccines cited *S. pneumoniae* as the most common documented bacterial pathogen, occurring in 4%–44% of all children investigated [14–16, 18].

In some studies, viral etiologies of CAP have been documented in up to 80% of children younger than 2 years; in contrast, investigations of older children, 10–16 years, who had both clinical and radiographic evidence of pneumonia, documented a much lower percentage of viral pathogens [15, 16, 18, 20]. Of viral pathogens, RSV is consistently the most frequently detected, representing up to 40% of identified pathogens in those younger than 2 years, but rarely identified in older children with CAP. Less frequently detected are adenoviruses, bocavirus, human metapneumovirus, influenza A and B viruses, parainfluenza viruses, coronaviruses and rhinovirus [14, 16, 18, 22, 23]. Epidemiologic investigations of hospitalized children with CAP

document that 2%–33% are simultaneously infected by 2 or more viruses [19, 20].

Epidemiologic studies that have assessed both viral and bacterial pathogens have reported bacterial pathogens isolated in 2%–50% of children with CAP; inpatient studies that enroll more seriously ill children often document higher rates of bacterial infection compared with outpatient studies [16, 17, 20, 21].

Pathogens responsible for "atypical pneumonia" have been identified in 3%–23% of children studied, with *M. pneumoniae* most often identified in older children and *C. pneumoniae* in infants [14–18]. Atypical pneumonia caused by *Mycoplasma* is characteristically slowly progressing, with malaise, sore throat, low-grade fever, and cough developing over 3–5 days. In contrast to adults with pneumonia, *Legionella* sp. has only rarely been identified in children [24].

Although CAP caused by *Mycobacterium tuberculosis* and the nontuberculous mycobacteria have been well-documented, the incidence of these serious infections in the United States is far less than that of viral or bacterial CAP and is often linked to high-risk exposures [25]. Likewise, fungal pneumonia in normal hosts caused by *Histoplasma*, *Coccidioides*, *Blastomyces,* and *Cryptococcus* is uncommon, and in most epidemiologic studies, children with fungal pneumonia are not identified. Mycobacterial and fungal pneumonia are not addressed in these guidelines.

Clinical Questions Addressed by the Expert Panel

Site-of-Care Management Decisions

I. When does a child or infant with CAP require hospitalization?

II. When should a child with CAP be admitted to an intensive care unit (ICU) or a unit with continuous cardiorespiratory monitoring?

Diagnostic Testing for Pediatric CAP

III. What diagnostic laboratory and imaging tests should be used in a child with suspected CAP in a clinic or hospital ward setting?

IV. What additional diagnostic tests should be used in a child with severe or life-threatening CAP?

Anti-Infective Treatment

V. Which anti-infective therapy should be provided to a child with suspected CAP in both the outpatient and inpatient settings?

VI. How can resistance to antimicrobials be minimized?

VII. What is the appropriate duration of antimicrobial therapy for CAP?

VIII. How should the clinician follow up the child with CAP for the expected response to therapy?

Adjunctive Surgical and Non–Anti-infective Therapy for Pediatric CAP

IX. How should a parapneumonic effusion be identified?

X. What factors are important in determining whether drainage of the parapneumonic effusion is required?

XI. What laboratory testing should be performed on pleural fluid?

XII. What are the drainage options for parapneumonic effusions?

XIII. When should VATS or open surgical decortication be considered in patients who have had chest tube drainage with or without fibrinolytic therapy?

XIV. When should a chest tube be removed either after primary drainage or VATS?

XV. What antibiotic therapy and duration is indicated for the treatment of parapneumonic effusion/empyema? (see also section on Anti-infective Treatment)

Management in the Child Not Responding to Treatment

XVI. What is the appropriate management of a child who is not responding to treatment for CAP?

XVII. How should the nonresponder with a pulmonary abscess or necrotizing pneumonia be managed?

Discharge Criteria

XVIII. When can a hospitalized child with CAP be safely discharged?

XIX. When is parenteral outpatient therapy indicated, in contrast to oral step-down therapy?

Prevention

XX. Can pediatric CAP be prevented?

There are many aspects to the clinical management of CAP and its complications (Table 2). Clinical practice recommendations regarding the daily management of children hospitalized with CAP, including intravenous fluid management, techniques for delivery of and monitoring oxygenation, and management of respiratory tract secretions as well as important economic and social issues were beyond the scope of this first edition of the pediatric CAP guidelines and were not addressed by the panel.

METHODOLOGY

Practice Guidelines

Practice guidelines are "systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [26]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [26].

Panel Composition

The Pediatric Infectious Diseases Society (PIDS) and the IDSA Standards and Practice Guidelines Committee (SPGC) convened experts in pediatric CAP from the fields of community pediatrics, public health, and the pediatric subspecialties of critical care medicine, emergency medicine, hospital medicine, infectious diseases, pulmonology, and surgery. Panel participants included representatives from the following collaborating organizations:

American Academy of Pediatrics (AAP), American College of Emergency Physicians, American Thoracic Society–Pediatric Section, Society for Hospital Medicine, the Society of Critical Care Medicine, and the American Pediatric Surgical Association. In addition, expert consultants in diagnostic microbiology including virology, and interventional radiology were asked to review and provide feedback on the draft guidelines.

Process Overview

As with other clinical practice guidelines developed by IDSA, a need for guidelines for pediatric CAP was demonstrated and the goals for the guidelines were similar to those for CAP in adults [27]. Clinical questions were developed by the writing group and approved by the IDSA SPGC. Computerized literature searches of the National Library of Medicine PubMed database were performed to identify data published through May 2010, although more recent articles with particular relevance to these guidelines have been included. Relevant abstracts from recent professional meetings and existing guidelines on pediatric CAP were also identified, collected, and reviewed.

As with all IDSA clinical practice guidelines initiated after 1 October 2008, the expert panel employed the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) method of assigning strength of recommendation and quality of the evidence to each recommendation (see Table 2) [3]. As applied to these guidelines, the writing group believes that in circumstances for which the quality of evidence is low or very low, there are likely to be situations in which even strong recommendations may not apply to specific subgroups within a population that is intended for that recommendation. For many conditions that lack moderate- or high-quality evidence, clinical judgment still plays an important role in management. Unfortunately, for many situations, current, prospectively collected, high-quality evidence was not available, highlighting the critical need for further investigation in order to establish a solid basis for future recommendations.

Consensus Development Based on Evidence

The expert panel met initially on 3 occasions via teleconference to complete the organizational work of the guideline, and in person at the 2009 Annual Meeting of the IDSA. Within the panel, subgroups were formed for each clinical question. Each subgroup reviewed the literature relevant to that clinical question and was responsible for drafting the recommendation(s) and evidence summaries for their assigned section. The drafts were circulated within the panel for commentary and discussed in additional conference calls and during a face-to-face meeting held in conjunction with the 2010 Pediatric Academic Societies meeting. Further refinement of the recommendations and evidence summaries occurred in 4 subsequent teleconference calls.

All members of the panel participated in the preparation and review of the draft guidelines. Feedback was solicited from external peer reviewers and from the organizations represented on the expert panel. These guidelines have been endorsed by the AAP, the American College of Emergency Physicians, the American Society of Microbiology, the American Thoracic Society, the Society for Hospital Medicine, and the Society of Critical Care Medicine. The guidelines were reviewed and approved by the PIDS Clinical Affairs Committee, the IDSA SPGC, the Council of the PIDS, and the Board of Directors of the IDSA before dissemination.

Guidelines and Conflict of Interest

All members of the expert panel complied with the IDSA policy on conflicts of interest that requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. They were given the IDSA conflicts of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. Potential conflicts are listed in the Acknowledgments section.

GUIDELINE RECOMMENDATIONS FOR MANAGEMENT OF CAP IN INFANTS AND CHILDREN

Site-of-Care Management Decisions

I. When Does a Child or Infant With CAP Require Hospitalization?

Recommendations

1. Children and infants who have moderate to severe CAP as defined by several factors, including respiratory distress and hypoxemia (sustained SpO_2, <90 % at sea level) (Table 3) should be hospitalized for management including skilled pediatric nursing care. *(strong recommendation; high-quality evidence)*
2. Infants <3–6 months of age with suspected bacterial CAP are likely to benefit from hospitalization. *(strong recommendation; low-quality evidence)*
3. Children and infants with a suspicion or documentation of CAP caused by a pathogen with increased virulence, such as CA-MRSA, should be hospitalized. *(strong recommendation; low-quality evidence)*
4. 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 should be hospitalized. *(strong recommendation; low-quality evidence)*

Evidence Summary

These guidelines are primarily designed to address infants and children living in the United States, with reasonable access to healthcare. The history, presentation, and examination of the child are the major determinants of the severity of the illness and the appropriate level of care with respect to outpatient or inpatient management. The physician's overall assessment of the child's status, at the time of examination and the anticipated clinical course should determine the site of care. However, the guidelines writing group recognizes that data from chest radiography, pulse oximetry, or laboratory studies are used variably by practitioners to support medical decision making. For these guidelines, we define "simple pneumonia" as either bronchopneumonia (primary involvement of airways and surrounding interstitium), or lobar pneumonia involving a single lobe. "Complicated pneumonia" is defined as a pulmonary parenchymal infection complicated by parapneumonic effusions, multilobar disease, abscesses or cavities, necrotizing pneumonia, empyema, pneumothorax or bronchopleural fistula; or pneumonia that is a complication of bacteremic disease that includes other sites of infection.

For resource-poor regions of the world, the World Health Organization (WHO) defines pneumonia primarily as cough or difficult breathing and age-adjusted tachypnea: (age 2–11 months, ≥50/min; 1–5 years, ≥40/min; ≥5 years, >20 breaths/min) [5]. Furthermore, severe pneumonia is defined as "cough or difficulty breathing plus one of the following: lower chest indrawing, nasal flaring, or grunting." Very severe pneumonia is defined as "cough or difficulty breathing plus one of the following: cyanosis, severe respiratory distress, inability to drink or vomiting everything, or lethargy/unconsciousness/convulsions." Such definitions of various levels of severity and studies to validate interventions for each level of severity are not well characterized for children living in resource-rich areas of the world.

At the more severe end of the spectrum of clinical presentation, most experts and professional societies recommend that any child or infant with respiratory distress (Table 3) should be admitted to the hospital for management [28–31]. Comparative studies from the developed world, evaluating the outcomes of children with various degrees of respiratory distress who are managed as outpatients compared with those managed as inpatients, have not been published. A "toxic appearance," which is not well defined but is represented by the components provided in Table 3, is universally accepted as an indication for admission to the hospital [28, 29].

In the past few decades, many consensus guidelines and clinical decision rules have been proposed for adults with CAP [27, 32–38]. There are multiple adult studies that describe scoring systems that have been demonstrated to be useful in predicting both which adults should be hospitalized and which adults require intensive care [27, 32–38]. Unfortunately, these scoring systems have not been validated in children and do not consider pediatric comorbid conditions, developmental stage, or psychosocial factors that influence the treating clinician's decision on the site of treatment for pediatric patients with CAP [39].

Validated scoring systems to predict which children with pneumonia should be hospitalized do not exist. Scores to predict mortality in critically ill children hospitalized in pediatric ICUs have existed for 2 decades [40]. Severity of illness scores built upon multiple logistic regression models, such as the Pediatric Risk of Mortality score and the Pediatric Index of Mortality predict the risk of death for children in ICU settings. These may facilitate outcome prediction in the ICU but do not reliably help the clinician to discriminate severity of illness in the less acutely ill child, thereby limiting utility in level-of-care decision making [41–44].

More directly relevant to evaluating severity of disease in CAP is the simple measurement of oxygenation by pulse oximetry. Hypoxemia is well established as a risk factor for poor outcome in children and infants with any type of disease, especially respiratory diseases. The use of pulse oximetry to detect hypoxemia has confirmed this relationship such that guidelines and clinical decision rules usually recommend pulse oximetry in any patient with pneumonia. In the developing world, for pediatric patients with nonsevere pneumonia (as defined by WHO), a pulse oximetric SpO_2 measurement of <90% at the initial visit has been documented to be predictive of failure of outpatient oral amoxicillin treatment [45]. In adults, hypoxemia is an indicator for respiratory failure requiring ICU admission in patients with pneumonia [46, 47] and has also been independently associated with short-term mortality [32, 48]. Widespread agreement exists that admission is indicated in a previously healthy child with CAP and an oxygen saturation in room air (at sea level) of <90%, although some would hospitalize children who have oxygen saturations as high as 93% [49]. At higher altitudes, lower oxygen saturations may be more appropriate to define respiratory failure, as demonstrated in Bolivia [50].

Clinical surrogates exist for adequate oxygenation, or, conversely, for hypoxemia and severe pneumonia. The child or infant's overall general assessment and ability to be consoled usually denote normal oxygenation [51]. "A moderate or severe alteration of general status" was an independent risk factor for death in children hospitalized in the developing world with an acute LRTI [52]. Although cyanosis may sometimes be difficult to detect, its presence denotes severe hypoxemia [52]. A systematic review of published studies, primarily in the developing world, found that central cyanosis had a higher specificity for predicting hypoxemia in children than other signs [53].

Tachypnea is a nonspecific clinical sign, but may represent a marker for respiratory distress and/or hypoxemia. "Rapid breathing as perceived by the mother" was statistically associated with hypoxemia in a study of children with pneumonia [50]. An increase in the age-specific respiratory rate or tachypnea has been linked to treatment failure in children with severe pneumonia in the developing world [54]. Although tachypnea in infants with pneumonia may correlate with presence of hypoxemia, tachypnea may also be caused by fever, dehydration, or a concurrent metabolic acidosis [55]. In a study from a pediatric emergency department in Boston of children <5 years old undergoing chest radiography for possible pneumonia, the respiratory rates for those with documented pneumonia did not differ significantly from those for children without pneumonia. However, of children with WHO-defined tachypnea, 20% had confirmed pneumonia, compared with 12% without tachypnea [56].

Retractions and grunting have also been found to be indicators of increased severity of LRTIs in children hospitalized in Argentina [57]. Retractions, whether intercostal, suprasternal or subcostal indicate a greater severity of pneumonia [29]. Nasal flaring and "head bobbing" have also been statistically associated with hypoxemia [50].

Dehydration, vomiting, or inability to take oral medication are additional considerations for hospitalization. Children in whom oral outpatient antimicrobial therapy has been attempted unsuccessfully and who demonstrate new and progressive respiratory distress (Table 3) will most often require hospitalization. Furthermore, those with psychosocial concerns, such as noncompliance with therapy or lack of reliable follow-up for any reason, may warrant admission [28, 29, 31]. Studies from both the United States [58] and Canada [59] found that children and infants with pneumonia were more likely to be hospitalized if they were of lower socioeconomic status. This may be attributed, in part, to nonmedical issues, including inaccessibility to adequate outpatient services.

Children with pneumonia caused by CA-MRSA, as described in case series, have a high incidence of necrotizing pneumonia and frequently require ICU admission [60, 61]. In a retrospective study of both adults and children with Panton-Valentine leukocidin–positive *S. aureus* CAP, 78% required mechanical ventilation [43]. If there is high suspicion for or documentation of CA-MRSA as a causative organism, the clinician should hospitalize the child for treatment with parenteral antimicrobial therapy and close observation, even if the respiratory symptoms are not severe at the time of initial evaluation.

The presence of significant comorbid conditions is also a risk factor for the development of pneumonia; the presence of pneumonia often results in a worsening of the underlying condition. In Dallas, Texas, 20% of children admitted with CAP had comorbid conditions, including reactive airway disease, genetic syndromes, and neurocognitive disorders [17]. Tan and colleagues from 8 pediatric tertiary care centers found that 36% of children hospitalized for pneumococcal pneumonia had underlying comorbid conditions that also included immunologic disorders and hematologic, cardiac, and chronic pulmonary conditions [62]. Children with a comorbid condition and influenza infection are more likely to require hospitalization than otherwise healthy children [23, 63, 64]. Although children who have chronic conditions may be at greater risk of pneumonia, these conditions are extremely diverse, so specific management issues for comorbid conditions will not be addressed in these guidelines [65, 66].

Young age is an additional risk factor for severity of pneumonia and need for hospitalization. The incidence of pneumonia and risk of severe pneumonia are greater in infants and young children. The attack rates are ~35–40 per 1000 infants (age, <12 months), 30–35 per 1000 preschool-aged children (2–5 years), 15 per 1000 school-aged children (5–9 years), and 6–12 per 1000 children >9 years old [67]. Furthermore, infants and young children tend to have more severe pneumonia with a greater need for hospitalization and a higher risk of respiratory failure. One independent risk factor for death in children hospitalized for acute respiratory tract infections in the Central African Republic was age between 2 and 11 months [52]. However, malnutrition may also contribute to severity of disease in the developing world, tempering conclusions about mortality in this age group from respiratory tract disease alone [68]. A clinical tool designed to predict which child with severe pneumonia would have failure of oral antimicrobial therapy in the developing world found that the age of the child was one of the most important clinical predictors (highly significant for those <6 months of age) [54]. In the developed world, prospectively collected data have not been published documenting a cutoff age below which hospitalization is necessary for improved outcomes. In the United States, very young infants (up to 3 months of age) with CAP are generally admitted to the hospital for initial management. Given the increased risk of morbidity, the admission of infants up to 6 months of age with suspected bacterial CAP is also prudent [29, 69].

II. When Should a Child with CAP Be Admitted to an Intensive Care Unit (ICU) or a Unit With Continuous Cardiorespiratory Monitoring?

Recommendations

5. A child should be admitted to an ICU if the child requires invasive ventilation via a nonpermanent artificial airway (eg, endotracheal tube). *(strong recommendation; high-quality evidence)*

6. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child acutely requires use of noninvasive positive pressure

ventilation (eg, continuous positive airway pressure or bilevel positive airway pressure). *(strong recommendation; very low-quality evidence)*

7. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child has impending respiratory failure. *(strong recommendation; moderate-quality evidence)*

8. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child has sustained tachycardia, inadequate blood pressure, or need for pharmacologic support of blood pressure or perfusion. *(strong recommendation; moderate-quality evidence)*

9. A child should be admitted to an ICU if the pulse oximetry measurement is ≤92% with inspired oxygen of ≥0.50. *(strong recommendation; low-quality evidence)*

10. A child should be admitted to an ICU or a unit with continuous cardiorespiratory monitoring capabilities if the child has altered mental status, whether due to hypercarbia or due to hypoxemia as a result of pneumonia. *(strong recommendation; low-quality evidence)*

11. Severity of illness scores should not be used as the sole criterion for ICU admission but should be used in the context of other clinical, laboratory, and radiologic findings. *(strong recommendation; low-quality evidence)*

Evidence Summary

When a child requires hospitalization for CAP, the clinician needs to consider the capabilities of the accepting facility or unit. Variations in the level of monitoring and in the skills of the bedside providers (nurse, respiratory therapist, and physician) will influence the decision on where to effectively monitor and treat the ill child. Appropriate placement of the ill child with increased work of breathing, tachypnea, or hypoxemia optimizes the use of ICU and general care area resources. Consultation with a specialist in pediatric critical care medicine is recommended if there is any concern regarding appropriate patient placement based on severity of disease (Table 4). ICU-level care is not typically required for children with CAP. However, in a study from Dallas, Texas, 6.5% of children hospitalized with CAP required mechanical ventilation [17], and 1.3% of children with CAP died, although almost one-third had comorbid conditions. A greater proportion of those with mixed bacterial and viral infections required mechanical ventilation (8.3%); mortality was 5.6% in this subgroup of children hospitalized with CAP [17].

Hypoxemia is present in many children with CAP, and in many cases low-flow supplemental oxygen provided by nasal cannula or face mask will suffice to restore oxygenation saturation for management on a hospital ward. Children requiring a fraction of inspired oxygen (FiO_2) of ≥0.50 to maintain saturation >92% should be cared for in a unit capable of continuous cardiorespiratory monitoring and rapid response should the clinical situation worsen. Other signs of respiratory distress and potential respiratory insufficiency include increased work of breathing (as evidenced by retractions [suprasternal, subcostal, or intercostals]), nasal flaring, and use of accessory muscles), recurrent apnea, or grunting. Grunting, when present, is a sign of severe disease and impending respiratory failure [71]. Oxygen saturation by pulse oximetry is usually monitored continuously for a child with increased work of breathing or significant distress, particularly if he or she has a decreased level of activity or agitation [51].

The child's overall clinical appearance and behavior may predict as much about the severity of illness as any score available. The exclusive use of severity of illness scores at hospital admission does not reliably provide the clinician with enough data to determine the need for ICU-level care.

The arterial oxygen pressure PaO2/FiO2 ratio provides an indication of the degree of respiratory insufficiency and impaired oxygen diffusion and, in conjunction with clinical examination, will enhance the determination of illness severity. This test requires an arterial blood gas determination of the PaO2, so its use is warranted only in evaluation of severe CAP with interpretation of the PaO2/FiO2 ratio by a physician experienced in treating children with respiratory failure.

The severity of pneumonia and need for ICU admission may be defined in part by the etiology. In a retrospective review of children admitted to a pediatric tertiary care center with invasive pneumococcal infection, those with concurrently positive viral studies (influenza, rhinovirus, adenovirus, RSV), were admitted to pediatric ICU more frequently and found to have longer pediatric ICU stays [72]. In 2 retrospective case series of pediatric patients, CA-MRSA pneumonia has been shown to have a high incidence of necrotizing pneumonia, a need for ICU care, and high associated mortality [60, 61].

DIAGNOSTIC TESTING FOR PEDIATRIC CAP

III. What Diagnostic Laboratory and Imaging Tests Should Be Used in a Child With Suspected CAP in an Outpatient or Inpatient Setting?

Recommendations

Microbiologic Testing

Blood Cultures: Outpatient

12. Blood cultures should not be routinely performed in nontoxic, fully immunized children with CAP managed in the outpatient setting. *(strong recommendation; moderate-quality evidence)*

13. Blood cultures should be obtained in children who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration after initiation of antibiotic therapy *(strong recommendation; moderate-quality evidence)*.

Blood Cultures: Inpatient

14. Blood cultures should be obtained in children requiring hospitalization for presumed bacterial CAP that is moderate to severe, particularly those with complicated pneumonia. *(strong recommendation, low-quality evidence)*

15. 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. *(weak recommendation; low-quality evidence)*

Follow-up Blood Cultures

16. Repeat blood cultures in children with clear clinical improvement are not necessary to document resolution of pneumococcal bacteremia. *(weak recommendation; low-quality evidence)*

17. Repeat blood cultures to document resolution of bacteremia should be performed in children with bacteremia caused by *S. aureus*, regardless of clinical status. *(strong recommendation; low-quality evidence)*

Sputum Gram Stain and Culture

18. Sputum samples for culture and Gram stain should be obtained in hospitalized children who can produce sputum. *(weak recommendation; low-quality evidence)*

Urinary Antigen Detection Tests

19. Urinary antigen detection tests are not recommended for the diagnosis of pneumococcal pneumonia in children; false-positive results are common. *(strong recommendation; high-quality evidence)*

Testing For Viral Pathogens

20. Sensitive and specific tests for the rapid diagnosis of influenza virus and other respiratory viruses should be used in the evaluation of children with CAP. A positive influenza test result may both decrease the need for additional diagnostic studies and decrease antibiotic use, while guiding appropriate use of antiviral agents in both outpatient and inpatient settings. *(strong recommendation; high-quality evidence)*

21. Antibacterial therapy is not necessary for children, either outpatients, or inpatients, with a positive test result for influenza virus in the absence of clinical, laboratory, or radiographic findings that suggest bacterial coinfection. *(strong recommendation; high-quality evidence)*

22. 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 coinfection. *(weak recommendation; low-quality evidence)*

Testing for Atypical Bacteria

23. Children with signs and symptoms suspicious for *M. pneumoniae* should be tested to help guide antibiotic selection. *(weak recommendation; moderate-quality evidence)*

24. Diagnostic testing for *C. pneumoniae* is not recommended as reliable, and readily available diagnostic tests do not currently exist. *(strong recommendation; high-quality evidence)*

Ancillary Diagnostic Testing

Complete Blood Cell Count

25. Routine measurement of the complete blood cell count is not necessary in all children with suspected CAP managed in the outpatient setting, but for those with more serious disease it may provide useful information for clinical management in the context of the clinical examination and other laboratory and imaging studies. *(weak recommendation; low-quality evidence)*

26. A complete blood cell count should be obtained for patients with severe pneumonia, to be interpreted in the context of the clinical examination and other laboratory and imaging studies. *(weak recommendation; low-quality evidence)*

Acute-Phase Reactants

27. Acute-phase reactants such as the ESR, CRP, or serum procalcitonin cannot be used as the sole determinant to distinguish between viral and bacterial causes of CAP. *(strong recommendation; high-quality evidence)*

28. Acute-phase reactants need not be routinely measured in fully immunized children with CAP who are managed as outpatients, although for more serious disease, they may provide useful information for clinical management. *(strong recommendation; low-quality evidence)*

29. In patients with more serious disease, such as those requiring hospitalization or those with pneumonia-associated complications, acute-phase reactants may be used in conjunction with clinical findings to assess response to therapy. *(weak recommendation; low-quality evidence)*

Pulse Oximetry

30. Pulse oximetry should be performed in all children with pneumonia and suspected hypoxemia. The presence of hypoxia should guide decisions regarding site of care and further diagnostic testing. *(strong recommendation; moderate-quality evidence)*

Chest Radiography

Initial Chest Radiographs: Outpatient

31. Routine chest radiographs are not necessary for the confirmation of suspected CAP in patients well enough to be

treated in the outpatient setting (after evaluation in the office, clinic, or emergency department setting). *(strong recommendation; high-quality evidence)*

32. Chest radiographs, posteroanterior and lateral, should be performed in patients with suspected or documented hypoxemia or significant respiratory distress (Table 3) and in patients with failed initial antibiotic therapy to verify the presence or absence of complications of pneumonia, including parapneumonic effusions, necrotizing pneumonia, and pneumothorax. *(strong recommendation; moderate-quality evidence)*

Initial Chest Radiographs: Inpatient

33. Chest radiographs (posteroanterior and lateral) should be obtained in all patients hospitalized for management of CAP to document the presence, size, and character of parenchymal infiltrates and identify complications of pneumonia that may lead to interventions beyond antimicrobial agents and supportive medical therapy. *(strong recommendation; moderate-quality evidence)*

Follow-up Chest Radiographs

34. Repeat chest radiographs are not routinely required in children who recover uneventfully from an episode of CAP. *(strong recommendation; moderate-quality evidence)*

35. A repeated chest radiograph should be obtained in children who fail to demonstrate clinical improvement and in those who have progressive symptoms or clinical deterioration within 48–72 hours after initiation of antibiotic therapy. *(strong recommendation; moderate-quality evidence)*

36. Routine daily chest radiography is not recommended in children with pneumonia complicated by parapneumonic effusion after chest tube placement or after VATS, if they remain clinically stable. *(strong recommendation; low-quality evidence)*

37. Follow-up chest radiographs should be obtained in patients with complicated pneumonia with worsening respiratory distress or clinical instability or in those with persistent fever that is not responding to therapy over 48–72 hours. *(strong recommendation; low-quality evidence)*

38. 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 on initial chest radiography with suspicion of an anatomic anomaly, chest mass, or foreign body aspiration. *(strong recommendation; moderate-quality evidence)*

Evidence Summary

An accurate and rapid diagnosis of the pathogen responsible for CAP provides for informed decision making, resulting in improved care with focused antimicrobial therapy, fewer unnecessary tests and procedures, and, for those who are hospitalized, potentially shorter inpatient stays. Unfortunately, in the diagnosis of CAP, particularly bacterial CAP, there are no single diagnostic tests that can be considered the reference standard [73].

Microbiologic Testing

Microbiologic testing, when recommended, is intended to identify a pathogen so that narrow-spectrum antimicrobial therapy directed at a specific bacterium or virus can be initiated. The narrowest treatment possible is considered ideal, because it will most often lead to less antimicrobial pressure for the selection of resistance, fewer adverse drug reactions, and reduced costs.

Blood Cultures: Outpatient

Blood cultures, when positive, provide documentation of the causative agent and important epidemiologic data; however, most blood cultures obtained from fully immunized children with nonsevere pneumonia are sterile. Furthermore, cultures of blood fail to detect many important causes of childhood CAP, including *M. pneumoniae* and all viral pathogens. Therefore, blood cultures help define the etiology in only a small proportion of children with CAP who are treated as outpatients.

Most current studies of blood cultures in the outpatient evaluation of children with CAP were conducted after licensure of the *H. influenzae* type b conjugate vaccine and before licensure of PCV7. In these studies, blood cultures were positive for pathogenic bacteria in <2% of patients with pneumonia who were well enough to be managed in the outpatient setting [74–78]. In a randomized trial of PCV7, blood cultures were positive in <1% of vaccine recipients who developed pneumonia [79]. The rate of detection of "true-positive" cases of bacteremia in children with CAP managed in the outpatient setting is lower than the rate of "false-positive" blood cultures reported in studies of childhood CAP (1.0%–8.2%) [74, 77, 80] and in studies evaluating the role of blood cultures in the emergency department evaluation of young children with fever (1.2%–2.8%) [81–84]. It is not known to what extent this relationship is attributable to the effect of preculture antibiotics, inadequate blood culture technique, insufficient blood volume for culture, or some combination of these factors [85–87]. Blood volumes sampled for bacterial culture in infants and children are less than those in adults. Most published series used FDA-approved pediatric blood culture diagnostic tests, optimized for 2-3 ml of blood, but children were included in data analyses if blood volumes were as low as 0.5 ml [75, 80-82].

Blood Cultures: Inpatient

In contrast to evaluation for outpatients, blood cultures are more frequently positive for pathogenic bacteria in children requiring hospitalization for CAP, with reported rates ranging from 1.4% to 3.4% in most studies [74, 78, 80, 88]. However, investigators in Utah, using stringent criteria for bacterial CAP, reported that 11.4% of blood cultures were positive in patients requiring hospitalization for CAP [89] with half of the

organisms identified as *S. pneumoniae*, serotype 1, a serotype not included in PCV7 but present in the 13-valent formulation (PVC13). Blood cultures were not routinely performed in all children hospitalized with CAP in prior studies [74, 78, 88, 89]. It is likely that blood cultures were performed disproportionately in children with greater illness severity; thus, these prior studies may overestimate the true rate of bacteremia in children hospitalized with uncomplicated CAP. Among patients with pneumonia complicated by parapneumonic effusion, rates of bacteremia also vary, ranging from 13.0% to 26.5% [80, 89–93]. The prevalence of bacteremia was 7.8% (95% confidence interval, 2.2%–18.9%) among children with any pneumonia-associated complication, including sepsis and organ dysfunction [80].

Despite the low overall yield of blood cultures in patients who require hospitalization, knowledge of the causative organism provides information that allows the treating physician to target antibiotic therapy to the causative agent. Culture-directed antimicrobial selection may be associated with improved clinical outcomes in only a minority of pediatric cases, as has been shown in studies of adults with CAP [94–96]. In contrast to adults with CAP, in whom positive blood cultures infrequently affect clinical management [97], positive blood cultures did result in narrowing or broadening of therapy in 5 of 6 patients with positive cultures, among 291 children from whom blood cultures were obtained [80]. However, the overall impact of blood cultures on clinical management may be small because of the low prevalence of bacteremia. In addition, it is worth noting that epidemiologic data derived from blood culture results have been essential in creating an evidence-based pneumococcal vaccination policy in the United States [98, 99].

When blood cultures are positive because of contaminant nonpathogenic bacteria (ie, false-positive cultures), results may lead to unnecessary broadening of antibiotic therapy. It may be difficult to determine whether broader therapy contributed to a patient's clinical improvement or led to a prolonged, inappropriate treatment course. The cost-effectiveness of obtaining blood cultures in all children hospitalized with CAP is not known.

Sputum Gram Stain and Culture

Gram stain and culture of expectorated sputum are recommended for adults hospitalized with CAP [27]. These tests are infrequently performed in children with CAP, because children cannot always provide adequate specimens for testing. Gram stain and culture of expectorated sputum should be attempted in older children and adolescents with more severe disease, including inpatients, or in those in whom outpatient therapy has failed. Better diagnostic tests are needed, particularly for children with nonsevere pneumonia, in whom the benefits of aggressive, invasive diagnostic procedures may not be worth the risk to the child.

Urinary Antigen Detection Tests

Urinary antigen tests for the detection of *S. pneumoniae* correlate well with sputum culture for *S. pneumoniae* [100, 101] in adults, and therefore antigen detection is routinely used to diagnose pneumococcal pneumonia in adults [27]. In children, urine antigen tests were positive in 47 of 62 (76%) with lobar pneumonia [102]; however, because the etiology of pneumonia could not be confirmed, the relevance of this finding is not clear. Of even greater concern, positive results occurred in 15% of febrile children without evidence of invasive pneumococcal disease; it was not clear whether these were false-positive results attributable to pneumococcal nasopharyngeal colonization or true-positive results in the context of early pulmonary disease that did not produce characteristic radiographic findings or whether they were associated with spontaneously resolved pneumococcal infection [102]. Dowell et al found no significant difference in the proportion of positive pneumococcal urinary antigen results (~35%) in children with pneumonia compared with children with dermatitis or diarrhea; however, a positive result was strongly associated with pneumococcal colonization [103]. Other studies also suggest that positive results can be attributed to nasopharyngeal colonization with *S. pneumoniae* in >15% of children [104, 105]. Positive results of pneumococcal urinary antigen tests do not reliably distinguish children with pneumococcal pneumonia from those who are merely colonized. In the absence of a true reference standard, there is insufficient information on the negative predictive value of this test to recommend its use for excluding pneumococcal disease.

Testing For Viral Pathogens

There is substantial evidence that the risk of serious bacterial infection is low in children with laboratory-confirmed viral infection [106–112]. However, the diffuse lower respiratory tract inflammation induced by viral respiratory tract infections predisposes to bacterial superinfection, making it difficult to exclude concurrent bacterial pneumonia with certainty in children with laboratory-confirmed viral infections. Viral and bacterial coinfections were detected in 23% of children with pneumonia evaluated at a tertiary-care children's hospital [17].

Randomized clinical trials [106, 107] and prospective studies [108–110] of rapid influenza testing demonstrate significant reductions in ancillary testing and antibiotic use among children evaluated in the emergency department during influenza season. Bonner et al enrolled 391 patients (aged 2 months to 21 years) with fever and influenzalike illness [106]. Rapid influenza tests were performed on nasopharyngeal specimens for all patients, with 52% positive for influenza. Patients were then randomized so that the treating physician was either provided or not provided with the results of influenza testing. Antibiotics were prescribed to 7.3% of patients for whom the physician was aware of a positive influenza test result, compared with 24.5% of patients for whom the physician was not aware of the results. Similar reductions were noted in the performance of chest radiography and other ancillary tests. No patient had lobar pneumonia [106]. Esposito et al [107] randomized 957 children

who presented to their clinic with influenzalike illness to rapid influenza testing or no testing, with 43 (8.9%) children testing positive. Antibiotics were prescribed to 32.6% of influenza-positive compared with 64.8% of influenza-negative patients; of those who were randomized to no testing, 61.8% were given antibiotics. No significant difference was noted in the performance of chest radiographs between groups. In a retrospective cohort study of hospitalized adults with laboratory-confirmed influenza infection, a positive rapid influenza test result was associated with 6-fold higher odds to discontinue or withhold antibiotic therapy compared with influenza-positive patients whose diagnosis was delayed because positive PCR results were not readily available [112].

Doan et al conducted an open-label randomized controlled trial in which children 3–36 months of age were randomized to receive a multiviral rapid diagnostic test by direct immunofluorescence assay (IFA) (n = 90) or routine care (n = 110) [111]. At least one virus was detected in 66% of patients randomized to viral testing. Differences in antibiotic prescribing or in the performance of chest radiography or other ancillary tests between virus-positive and virus-negative or untested patients were not statistically significant. However, patients undergoing viral testing were less likely to receive antibiotics when subsequently seeing their primary care physician for the same illness within 1 week of discharge from the emergency department. In a retrospective review, Byington and colleagues documented a significant decrease in antibiotic prescribing, with respect to inpatient intravenous therapy and oral antibiotic therapy at discharge, for hospitalized children who tested positive for RSV, parainfluenza 1, 2, 3, or adenovirus, compared with those who tested negative [113].

Although positive tests for viral pathogens are helpful, the sensitivity and specificity of rapid viral tests are not 100%, and false-negative and false-positive tests occur. For influenza, the sensitivity of each type of test varies by both method and sampling technique, and for the rapid tests, may also vary by the strains of influenza circulating in any given year. For example, the sensitivity of rapid influenza tests during 2009 pandemic H1N1 was poor compared with the performance of tests for seasonal influenza [114]. For children with influenzalike illness in a community with documented influenza virus circulation, a negative rapid influenza virus test in a child with CAP and symptoms compatible with influenza may reflect inaccuracies of the test, rather than reliably excluding influenza virus as a pathogen. For children with influenza, particularly those who require mechanical ventilation, initial results of nasopharyngeal testing for influenza may be negative, even with reverse-transcriptase PCR techniques, because of many factors, including poor-quality specimens, sampling of the upper rather than lower respiratory tract, and prolonged duration from illness onset to specimen collection. Multiple specimens on multiple days may be required for diagnosis. Because early influenza antiviral therapy provides the greatest benefit to the child, a clinician should not wait to start empiric antiviral therapy until after obtaining respiratory tract samples for diagnosis [115, 116].

Some children with viral LRTI may also have an associated bacterial LRTI. In a study of 23 seriously ill, ventilated infants with documented RSV CAP, Levin et al found that 39% had specimens suggestive of concomitant bacterial infection based on tracheal aspirate cultures. They concluded from their patients and a literature review that evidence of bacterial pneumonia in otherwise low-risk infants with RSV presenting with respiratory failure is present in ≥20%, and the use of empiric antibiotics for 24–48 hours pending culture results may be justified until concomitant bacterial infection is excluded [117]. However, for infants who do not have respiratory failure or any other findings that suggest bacterial coinfection, care process models have the potential to decrease inappropriate antibiotic use when they discourage such use in children who are documented to have a positive rapid test for a respiratory virus.

Testing for Atypical Bacteria

The precise role of testing and treating for *M. pneumoniae* LRTI in children is not well defined, because high-quality data on the natural history of disease and impact of treatment are not available. For younger children in particular, decisions regarding testing are made more difficult by uncertainty regarding the extent to which treatment of confirmed *M. pneumoniae* infections improves clinical outcomes in this population (see Evidence Summary for Recommendation 44). For treatment of CAP in children, it is important to minimize unnecessary prescribing of macrolide therapy, which may be inadequate for treatment of *S. pneumoniae*, while offering the best care for children with CAP caused by *M. pneumoniae*. Testing for *M. pneumoniae* may be most useful when the pretest probability for *M. pneumoniae* infection is intermediate or high. The age at which one should begin to strongly consider *M. pneumoniae* as the cause of CAP is not well defined. *M. pneumoniae* is increasingly being diagnosed serologically as a cause of LRTI in young children [15, 17, 18, 118–122]. Testing may not be necessary in children with a low likelihood of *M. pneumoniae* infection (eg, younger children with symptoms more compatible with a primary viral upper respiratory tract infection), in whom the positive predictive value of a positive test may only be modest (ie, false-positive results will occur). Testing may be most useful in guiding decisions regarding empiric antibiotic therapy in school-aged children and adolescents who have findings consistent with but not classic for *M. pneumoniae* infection. In these situations, a positive test result for *M. pneumoniae* may warrant treatment, whereas a negative result makes the diagnosis of *M. pneumoniae* pneumonia unlikely. Epidemiologic aspects of *M. pneumoniae* infection and commonly available tests are summarized below.

A variety of tests exist for detection of *M. pneumoniae* infections, including culture, cold agglutinating antibodies, serology, and molecular-based methods such as PCR assays, each with different performance characteristics (sensitivity, specificity, positive and negative predictive values). The complex nutritional requirements and slow growth of *M. pneumoniae* on culture media make its identification impractical for most laboratories; additionally, results from culture for *M. pneumoniae* are not available in a clinically relevant time frame. The presence of cold-reacting antibodies against red blood cells in the serum of patients with primary atypical pneumonia is well known [123]. Cold agglutinin titers >1:64 are present at the time of acute illness in ~75% of adults with pneumonia due to *M. pneumoniae*. Because the test is less well studied in children, its accuracy in detecting respiratory infection due to *M. pneumoniae* is not known. The specificity of a titer <1:64 is low because a variety of other respiratory tract pathogens provoke modest increases in cold agglutinins. Performance of the cold agglutinin test at the bedside lacks the rigorous standards of high sensitivity and specificity and reproducibility currently expected of medical diagnostics and is not recommended in any setting.

Serologic methods include complement fixation, enzyme-linked immunosorbent assays (ELISAs), and rapid enzyme immunoassay cards. Enzyme assays are less time consuming and have thus largely replaced complement fixation tests in the laboratory setting for detection of immunoglobulin (Ig) M. Rapid serologic tests typically have results available within 10 min. The ImmunoCard rapid IgM test (Meridian Bioscience) has been compared with other serology tests but not with PCR. Alexander et al studied 896 specimens submitted to clinical laboratories for *M. pneumoniae* serologic testing. When compared with 2 *M. pneumoniae* IgM-specific assays (IFA and ELISA) and a standard complement fixation procedure, the ImmunoCard had sensitivities ranging from 74% (compared with ELISA) to 96% (compared with complement fixation), with inconsistent results resolved using IFA as the reference standard [124]. ImmunoCard specificities ranged from 85% (compared with IgM-specific ELISA) to 98% (compared with IgM-specific IFA), with inconsistencies resolved using medical record review [124]. Results were similar in a subsequent study of 145 children referred for *M. pneumoniae* testing [125]. However, the specificity of IgM detection described during an outbreak of *M. pneumoniae* pneumonia was only 43% for children 10–18 years of age and 82% for those ≥19 years of age, compared with a case definition reference standard for diagnosis [126]. A combined IgG-IgM assay (Remel; Thermo Fisher Scientific) assessed during this outbreak had a higher specificity in children 10–18 years of age (74%) but a lower sensitivity (52%) compared with IgM detection (89%) [126]. An IgM assay (Platelia IgM capture; Sanofi Diagnostics) appears to be as sensitive as PCR for detection of *M. pneumoniae* in CAP in children [127]. Direct comparison of studies using PCR is difficult because specimens were obtained from different sites (eg, nasal wash, nasopharyngeal swab, throat, sputum) using different primer sets and amplification techniques [128–132], but PCR-based testing is neither readily available nor practical in office, emergency department, or community hospital settings using currently available test systems. In summary, we believe that testing for *Mycoplasma* infection is important to optimize use of macrolides in children. However, no single currently available test offers the sensitivity and specificity desired in a clinically relevant time frame. Therefore, the clinician should be knowledgeable regarding the performance characteristics of the tests offered by local laboratories.

None of the many diagnostic assays used worldwide to identify *C. pneumoniae* has received approval by the US Food and Drug Administration for clinical use. Recommendations for standardized approaches to culture, PCR testing, serology, and immunohistochemistry were published in 2001 by the CDC and the Canadian Laboratory Centres for Disease Control (LCDC) [133]. Serology has been the primary means of clinical diagnostic testing for *C. pneumoniae* because of its widespread availability and relative simplicity. However, many of the available assays, including complement fixation, whole inclusion fluorescence, and various enzyme immunoassays, perform poorly or have not been adequately validated; microimmunofluorescence testing remains the only endorsed approach [133]. During primary infection, IgM antibody appears 2–3 weeks after illness onset. IgG antibody may not reach a diagnostically high titer until 6–8 weeks after the onset of illness. Therefore, confirmation of primary acute infection requires documenting an IgM titer of 1:16 or greater or a 4-fold rise in IgG titer between acute and convalescent serum specimens. In case of reinfection, IgM antibody may not appear, and the level of IgG antibody titer may rise quickly within 1–2 weeks of infection [133]. IgG titers of 1:16 or greater are consistent with previous exposure and are seen in approximately half of adults. Therefore, a single elevated IgG titer does not confirm the diagnosis of *C. pneumoniae* infection. The organism or its DNA can be directly identified by means of culture or PCR testing in specimens from nasopharyngeal or throat swabs, sputum, blood, or tissue. Few published PCR assays met the validation criteria proposed by the CDC and LCDC [133]. In summary, no widely available and timely test exists for the diagnosis of *C. pneumoniae* infection.

Ancillary Diagnostic Testing

Complete Blood Cell Count

Results of a complete blood cell count with WBC differential may influence therapy in ill children. In addition to evaluation of WBCs, the presence of anemia or thrombocytopenia may guide subsequent therapeutic interventions and raise concern for hemolytic-uremic syndrome, a rare complication of

pneumococcal pneumonia [134–137]. The specificity of the WBC count in making the diagnosis of bacterial pneumonia is poor. Although the WBC count is elevated in many children with bacterial pneumonia, the degree of elevation does not reliably distinguish bacterial from viral infection [138]. A radiographic infiltrate has been detected in some children who present for medical care only with fever and leukocytosis in the absence of clinical signs of LRTI; the relevance of this finding of "occult" pneumonia is not clear [139–141]. Occult pneumonia is addressed in the Evidence Summary for Recommendation 31.

Acute-Phase Reactants

Acute-phase reactants, including peripheral WBC count with differential analysis, ESR, CRP, and procalcitonin do not reliably distinguish bacterial from viral infections when used as the sole diagnostic test. Korppi et al found that the WBC count, CRP, and ESR were significantly higher in children with pneumococcal pneumonia than in those with viral or atypical pneumonia [138]. However, the number of patients with pneumococcal disease, diagnosed most often by serology, was relatively small (n = 29), there was considerable overlap in values between the 2 groups, and the sensitivity and positive predictive value for their specified WBC count criteria for pneumonia were low. The sensitivities for a CRP >6.0 mg/dL or an ESR >35 mm/h were 26% and 25%, respectively, but increased when the 2 results were combined. The positive predictive value for a CRP >6.0 mg/dL or an ESR >35 mm/h was 43% and 38%, respectively [138]. Other Finnish investigators found wide variation in WBC count, CRP, and ESR values between children with CAP attributable to bacteria and viruses; the values did not differ significantly between the 2 groups [142]. Procalcitonin, although promising as a sensitive marker of serious bacterial infection, has limited value in distinguishing nonserious bacterial from viral pneumonia in children because the values are widely distributed. Elevated procalcitonin concentrations in children with documented viral infections raise the possibility that some children identified as having viral pneumonia may actually have a viral-bacterial coinfection [143–148]. However, low values may be helpful in distinguishing viral pneumonia from bacterial pneumonia associated with bacteremia [149]. Acute-phase reactants can also be measured at baseline for patients requiring hospitalization. Declining values of CRP or procalcitonin may correlate with improvement in clinical symptoms and thus have the potential to serve as objective measures of disease resolution.

Pulse Oximetry

Hypoxemia is well established as a risk factor for poor outcome in children and infants with systemic disease, especially respiratory diseases. Criteria associated with hypoxemia include those provided in Table 3. Oxygen saturation measurements provide a simple, reliable, noninvasive estimate of arterial oxygenation. Evidence supporting the routine use of pulse oximetry measurements is discussed in the Evidence Summary for Recommendation 1.

Chest Radiography

Initial Chest Radiographs

Chest radiographs cannot reliably distinguish viral from bacterial CAP and do not reliably distinguish among the various possible bacterial pathogens. Therefore, chest radiographs do not have a substantial impact on clinical outcomes [150–152]. In addition, it may be impractical to obtain chest radiographs, especially in the office setting. Studies have documented that chest radiographs performed in children with suspected acute LRTI led to changes in the diagnosis or the use of antibiotics in ~25% of children evaluated in a clinic or emergency department setting but rarely affected decisions regarding hospitalization [153, 154]. Chest radiographs in these studies were least useful when information from history and clinical examination were consistent with the diagnosis of pneumonia, suggesting that chest radiographs are not necessary in outpatients in whom the diagnosis of CAP is strongly suspected on the basis of clinical findings. In a study of the utility of chest radiographs, Alario and colleagues studied 102 children between 1 month and 18 years of age with fever or respiratory symptoms for whom a resident ordered a chest radiograph in an outpatient setting [153]. Before the chest radiograph was obtained, clinical assessments were performed, and management plans were recorded by an experienced attending physician. For the experienced physician, the chest radiographs supported the diagnosis of pneumonia in 11 of 12 patients (92%) with a preradiograph diagnosis of pneumonia [153]. The diagnosis of viral or bacterial pneumonia was made in an another 6 of 40 patients (15%) with a preradiograph diagnosis of "no LRTI" [153]. Data from a developing country also suggest that the changes in management resulting from chest radiographs in the outpatient setting are not typically associated with improved clinical outcomes [151, 155].

Radiographic infiltrates have been reported in ~5%–19% of children with fever in the absence of tachypnea, hypoxemia, respiratory distress, or signs of LRTI; this phenomenon has been referred to as "occult" pneumonia [139–141]. The proportion of children <5 years old who had occult pneumonia decreased from 15% before to 9% after recommendation for universal vaccination with PCV7 [141]. Clinical features associated with a higher likelihood of occult pneumonia included presence of cough, fever for >5 days, fever >39°C, and leukocytosis (WBC count >20 000/μL) [140]. Outcome data in the absence of antibiotic therapy is not available for these patients, making the relevance of the occult pneumonia diagnosis uncertain. Chest radiography, though not routinely required, should be performed in patients with prolonged fever and cough even in the absence of tachypnea or respiratory distress.

The rate of radiographically confirmed pneumonia among children with wheezing is low (4.9% overall), particularly in the absence of fever (2%) [156]. Among children with fever in the context of wheezing, radiographic infiltrates were detected in 6.9% of those without hypoxemia and in 20.6% of those with hypoxemia (defined as percutaneous oxygen saturation <92%) [156]. Therefore, chest radiography for the diagnosis of pneumonia is not routinely recommended in patients with wheezing in the absence of fever or hypoxemia.

Abdominal pain is occasionally the predominant presenting complaint in children with CAP, especially for those <5 years of age. Although routine chest radiographs are not necessary in children with abdominal pain, they should be considered in those with unexplained abdominal pain, especially in the context of tachypnea, cough, or fever [156, 157].

The evaluation of chest radiographs is subjective. As a consequence, there is variation even among experts regarding the presence or absence of radiographic features used for diagnosis of CAP [158–163]. There is greater consensus regarding the presence of alveolar consolidation compared with other radiographic features of pneumonia [159, 164, 165]. The WHO Vaccine Trial Investigators' Radiology Working Group has proposed standards for interpretation of pediatric chest radiographs for the diagnosis of pneumonia [166]. These standards include reporting of film quality, classification of specific findings, and explicit statements regarding radiograph interpretation. High agreement in identifying radiographically confirmed pneumonia was achieved using standardized definitions and training; the kappa index was >0.6 for 19 of 20 radiologists and clinicians in a review of 92 chest radiographs [166]. Identification of an infiltrate on chest radiograph by attending clinicians compared with radiologists does not consistently lead to meaningful differences in clinical management or outcomes [167]. Widespread adoption of standard definitions may facilitate comparison of future studies of childhood pneumonia.

Follow-up Chest Radiographs

Routine follow-up chest radiographs are not warranted in children who recover uneventfully from an episode of CAP. Radiologic abnormalities are known to lag behind clinical resolution. Follow-up chest radiographs obtained 3–6 weeks after initial imaging reveal persistent or residual abnormalities in 10%–30% of children with radiographically confirmed CAP [168–172]. Persistent abnormalities are more likely in patients with signs or symptoms of pneumonia at the time of follow-up radiography (up to 50% in one study) [168]; however, these abnormalities rarely alter clinical management. Few studies have systematically followed up children with radiographic abnormalities for extended periods of time. Radiographs performed 3–7 weeks after an episode of radiographically confirmed CAP revealed residual or new changes in 59 (30%) of 196 children; persistence of interstitial infiltrates and the interval development of atelectasis were the most commonly noted findings [169]. Long-term follow-up 8–10 years later did not reveal any illnesses attributable to the initial episode of CAP [169]. In a prospective study of adults hospitalized with severe CAP, chest radiographs were repeated 7 and 28 days after admission [173]. At day 7 and day 28, 75% and 47% of patients, respectively, still had abnormal findings. Delayed resolution of radiographic abnormalities was associated with multilobar disease, dullness to percussion at examination, higher CRP levels, and documented pneumococcal infection. However, delayed resolution of radiographic abnormalities did not portend failure of antimicrobial therapy or a worse clinical outcome. In summary, routine follow-up chest radiographs do not provide additional clinical value but represent unnecessary radiation exposure to infants and children.

A subset of patients, such as those with lobar collapse or recurrent pneumonia involving the same lobe, may benefit from repeat chest radiography. Pathology affecting a single region can be related to obstruction of the airway lumen to that region, to extrinsic compression of the airway, to intrinsic narrowing of the airway, or to an abnormality of the involved parenchyma, such as a chest mass, that may appear to represent pneumonia at imaging [174]. A detailed discussion of recurrent pneumonia is beyond the scope of this document.

IV. What Additional Diagnostic Tests Should Be Used in a Child With Severe or Life-Threatening CAP?

Recommendations

39. The clinician should obtain tracheal aspirates for Gram stain and culture, as well as clinically and epidemiologically guided testing for viral pathogens, including influenza virus, at the time of initial endotracheal tube placement in children requiring mechanical ventilation. *(strong recommendation; low-quality evidence)*

40. Bronchoscopic or blind protected specimen brush sampling, BAL, percutaneous lung aspiration, or open lung biopsy should be reserved for the immunocompetent child with severe CAP if initial diagnostic test results are not positive. *(weak recommendation; low-quality evidence)*

Evidence Summary

The infectious etiologies of CAP are diverse. Multiple common pathogens present with a spectrum of clinical disease from mild to life threatening. The clinician, when faced with a child with severe manifestations of CAP, should weigh the benefit of diagnostic modalities targeted to identify specific pathogens with the impact on management decisions. The goal of performing diagnostic testing is to obtain evidence of the causative pathogen in order to avoid unnecessary use of antibiotics and to provide optimal, pathogen-directed care for the child.

Tracheal aspirates are commonly obtained in the pediatric ICU by suctioning a specimen from the endotracheal tube using

a standard suction catheter and specimen trap. Blind tracheal aspirates may not adequately identify the pathogen of interest, because the catheter may collect organisms from sources other than infected lung during the procurement process, merely reflecting the organisms colonizing the endotracheal tube or trachea. For children with influenza virus as the suspected etiology of CAP, rapid PCR testing of pulmonary secretions obtained through an endotracheal tube may yield positive results when nasopharyngeal test results are negative [175].

BAL can provide quantitative data, but in the pediatric population the procedure is more complex because of patients' small airways, particularly for neonates. Flexible bronchoscopes with the ability to obtain samples through a suction port can be used for the child without intubation or the child with a preexisting endotracheal tube , particularly with newer ultrathin bronchoscopes. In general, flexible fiberoptic bronchoscopy and BAL, which is directed to an area of concern, is well tolerated in mechanically ventilated children; the BAL procedure does not result in significant reductions in PaO2/FiO2 ratios, nor an increase in adverse effects on blood pH or $PaCO_2$ arterial carbon dioxide pressure [176]. In Bar-Zohar and Sivan's series, 25 ventilated children had blind tracheal aspirates and subsequent BAL. The recovery of organisms by blind tracheal aspirate and BAL were not concordant. Blind tracheal aspirates before BAL were positive in 22 of 25 cases (88%), with negative BAL findings in 11 of these 22 aspirate-positive cases (50%). In only 4 patients (36%) were the organisms isolated identical from both techniques [176]. These investigators found that 50% of children had antimicrobial treatment changed as a consequence of the culture results from bronchoscopy. In a study of BAL in children with a variety of respiratory diagnoses, Tang and Chen found that a positive or negative culture resulted in a treatment change in 23.4% of their patients [177].

In a prospective study of 88 hospitalized adults with CAP, routine sputum culture followed by bronchoscopy with a protected specimen brush technique and then by BAL within the first 8 hours after admission revealed that BAL was the most sensitive; 37.5% had a positive conventional sputum culture, 64.7% had a positive protected specimen brush culture, and 73.8% had a positive BAL culture [178]. The advantage of using invasive techniques (bronchoscopic protected specimen brush and BAL, with quantitative microbiologic studies) was documented by Fagon et al in a prospective, randomized study including 413 ventilated adults. They demonstrated decreased usage of antibiotics and lower mortality rates as enhanced culture data from invasive techniques allowed for more pathogen-specific therapy [179]. Invasive techniques can decrease the number of cases treated incorrectly because of tracheal colonization, thus allowing a more judicious use of antimicrobials.

Standard protected specimen brush technique through a bronchoscope is not routinely used in ventilated children because it requires a larger bronchoscope, and thus a larger endotracheal tube [180]. However, blind protected BAL, can provide qualitative and quantitative cultures in children. Gauvin et al reported that this technique in ventilated children was reproducible and easy to perform at the bedside, yet complications were frequent. The majority of complications were minor and transitory, though 2 significant adverse events were reported (pneumothorax requiring a chest tube, and increased intracranial pressure) [181]. A similar technique, used in infants as young as 7 days, involves blindly inserting a double-sheathed protected specimen brush, to a point just beyond the endotracheal tube tip. The inner catheter is then extended 1 cm further and the protective plug expelled, allowing the brush to be advanced another 1-2 cm, and then retracted into the sheath and removed [182].

Other techniques for obtaining definitive cultures include percutaneous needle aspiration of the affected lung area. Vuori-Holopainen in a study of Finnish children with CAP used non–CT-guided aspiration at the bedside of 34 patients. Analysis of the aspirated samples provided a definitive diagnosis in 20 (59%) of 34 patients, with a total of 21 bacteria and 2 viruses identified. In the 26 patients from whom a return of fluid (adequate sample) was obtained, a pathogen was detected in 69%. Eighteen percent of the children had evidence of a pneumothorax on the post-procedure radiograph, although none required chest tube placement and all showed resolution with 3 days [183]. Imaging (CT or ultrasound)–guided percutaneous needle aspiration presents another option for direct culture of infected lung tissue [184].

Finally, for children with life-threatening CAP of unknown etiology, an open or thoracoscopic lung biopsy can be a useful, though high-risk, diagnostic procedure. A retrospective review of 31 children undergoing open lung biopsy demonstrated that in 76% the open lung biopsy led to a pertinent change in clinical management and in 80% of cases, open lung biopsy provided an infectious diagnosis, when a preceding BAL was inadequate. Of note, open lung biopsy was associated with a 45% complication rate, thereby limiting its use to critical situations [185].

ANTI-INFECTIVE TREATMENT

V. Which Anti-Infective Therapy Should Be Provided to a Child With Suspected CAP in Both Outpatient and Inpatient Settings?

Recommendations

Outpatients

41. Antimicrobial therapy is not routinely required for preschool-aged children with CAP, because viral pathogens are responsible for the great majority of clinical disease. *(strong recommendation; high-quality evidence)*

42. Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool-aged children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides

appropriate coverage for *S. pneumoniae,* the most prominent invasive bacterial pathogen. Table 5 lists preferred agents and alternative agents for children allergic to amoxicillin *(strong recommendation; moderate-quality evidence)*

43. Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized school-aged children and adolescents with mild to moderate CAP for *S. pneumoniae*, the most prominent invasive bacterial pathogen. Atypical bacterial pathogens (eg, *M. pneumoniae*) and less common lower respiratory tract bacterial pathogens, as discussed in the Evidence Summary, should also be considered in management decisions. *(strong recommendation; moderate-quality evidence)*

44. Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens. Laboratory testing for *M. pneumoniae* should be performed if available in a clinically relevant time frame. Table 5 lists preferred and alternative agents for atypical pathogens. *(weak recommendation; moderate-quality evidence)*

45. Influenza antiviral therapy (Table 6) should be administered as soon as possible to children with moderate to severe CAP consistent with influenza virus infection during widespread local circulation of influenza viruses, particularly for those with clinically worsening disease documented at the time of an outpatient visit. Because early antiviral treatment has been shown to provide maximal benefit, treatment should not be delayed for confirmation of positive influenza test results. Negative influenza diagnostic tests, especially rapid antigen tests, do not conclusively exclude influenza disease. Treatment after 48 hours of symptomatic infection may still provide clinical benefit to those with more severe disease. *(strong recommendation; moderate-quality evidence)*

Inpatients

46. Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with CAP when local epidemiologic data document lack of substantial high-level penicillin-resistance for invasive *S. pneumoniae.* Other antimicrobial agents for empiric therapy are provided in Table 7. *(strong recommendation; moderate-quality evidence)*

47. Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including empyema (Table 7). Non–β-lactam agents such as vancomycin have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. *(weak recommendation; moderate-quality evidence)*

48. Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *M. pneumoniae* and *C. pneumoniae* are significant considerations; diagnostic testing should be performed if available in a clinically relevant time frame (Table 7). *(weak recommendation; moderate-quality evidence)*

49. Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *S. aureus* (Table 7). *(strong recommendation; low-quality evidence)*

Evidence Summary

Most preschool-aged children with pediatric CAP, when tested with sensitive PCR techniques for respiratory viruses (such as rhinovirus, RSV, human metapneumovirus, parainfluenza viruses, influenza A and B viruses, adenovirus, coronavirus, and human bocavirus), and bacteria (including *S. pneumoniae, H. influenzae,* and *M. pneumoniae)* are found to be positive for respiratory viruses more often than for bacteria [20], although the sensitivity of molecular tests to diagnose viral pathogens currently exceeds that of conventional microbiologic tests for bacterial pathogens. In young children with clinical characteristics compatible with upper and lower respiratory tract viral infection, antibiotics are not helpful, may cause drug toxicity, and will facilitate the development of antimicrobial resistance.

Children with suspected bacterial CAP that is serious enough to warrant hospitalization should routinely be treated with parenteral antibiotics to provide reliable blood and tissue concentrations (Table 7). If the pathogen has been identified from blood culture or culture of an appropriately collected respiratory tract specimen, narrow-spectrum, safe, and effective therapy can be chosen. Before the widespread use of pneumococcal conjugate vaccines, ~1% of children with pneumococcal bacteremia were documented to also have bacterial meningitis. The clinician should be aware that the dosages of most antimicrobials, including all β-lactam agents, are greater for the child with meningitis than for the child with pneumonia.

Bacterial Pathogens in CAP

Empiric oral antimicrobial therapy for outpatients is designed to provide effective treatment for the bacterial pathogens most likely to cause LRTI, with particular emphasis on *S. pneumoniae*, which is both the most common bacterial pathogen and one that, when untreated or treated inadequately, may lead to serious sequelae [188]. Much less common lower respiratory tract pathogens such as nontypeable strains of *H. influenzae* do not

routinely require empiric therapy. Of more concern are LRTIs caused by *S. aureus* (including CA-MRSA), for which inpatient management and initial parenteral therapy may minimize morbidity and mortality rates.

Bacterial-viral coinfections have been well documented to occur with influenza virus and *S. pneumoniae, S. aureus* (both methicillin-susceptible and methicillin-resistant strains), and group A streptococcus. For some children, empiric therapy may require both antimicrobial and antiviral agents.

Streptococcus pneumoniae

For treatment of pneumococcal infections, penicillin G represents the most narrow-spectrum, effective antimicrobial agent. The interpretation of in vitro tests of susceptibility to penicillin has been revised recently, with the knowledge that higher doses of parenterally administered penicillin can achieve tissue concentrations that will be effective against organisms with minimum inhibitory concentrations (MICs) up to 2 μg/mL, may be effective for strains with MICs of 4 μg/mL, and are not likely to be effective for those with MICs of ≥8 μg/mL [189]. However, with clear limitations on the ability to absorb orally administered penicillin and its salts from the gastrointestinal tract, there has been no change in interpretation of MIC values for pneumococci treated with oral therapy: penicillin-susceptible strains remain defined as having MICs < 0.06 μg/mL, intermediately susceptible strains having MICs between 0.12 and 1.0 μg/mL, and resistant strains as having MICs ≥2.0 μg/mL. Compared with penicillin, amoxicillin displays more favorable pharmacokinetics and tolerability with respect to oral therapy. The doses of antimicrobials recommended for effective treatment are directly related to the susceptibility of the strains of *S. pneumoniae* being treated.

At the time of initial pediatric registration trials for amoxicillin in the early 1970s, the vast majority of isolates were highly susceptible, and "standard" dosage therapy (40–45 mg/kg/day divided into 3 equal doses) appeared to be uniformly successful. With the development of widespread pneumococcal resistance to penicillin in the 1990s, high-dosage amoxicillin (90 mg/kg/day) was studied in an attempt to overcome resistance in pneumococcus and found to be successful for acute otitis media when given twice daily [190]. The half-life of amoxicillin in middle ear fluid was documented to be 4–6 hours, compared with 1 hour in serum, providing supporting evidence for twice-daily dosing for acute otitis media. Similar prospective, comparative data supporting a recommendation for twice-daily dosing have not been collected for documented pneumococcal pneumonia in children [191]. To achieve the appropriate amoxicillin exposure in lung infected by relatively resistant pneumococci (MICs of 2.0 μg/mL), a high total daily dose (90 mg/kg/day) in 3 equally divided portions is predicted to achieve a clinical and microbiologic cure in about 90% of children treated, compared with only 65% of children treated with the same total daily dose divided into 2 equal doses [192]. However, for fully susceptible strains, a dosage of 90 mg/kg/day in 2 divided portions, as indicated for otitis media, is likely to be successful [193]. With the success of the 7-valent pneumococcal vaccine in decreasing invasive pneumococcal infection, a decrease in the degree of penicillin resistance in circulating strains has been documented [194], suggesting that the appropriate dosage of amoxicillin may decrease to that recommended in the prevaccine era. However, with the emergence of antibiotic-resistant serotype 19A strains of pneumococcus, most experts believe that, when pneumococcal pneumonia is suspected and oral therapy is appropriate, high-dosage amoxicillin is still preferred. Although serotype 19A is included in the newer 13-valent pneumococcal vaccine, it is too soon to evaluate the impact of this intervention on invasive disease or on the emergence of antibiotic resistance to non-PCV13 serotypes.

Although amoxicillin has a broader spectrum of activity than penicillin, it is recommended for oral therapy of pneumonia caused by *S. pneumoniae* owing to better absorption from the gastrointestinal tract yielding higher serum concentrations (with the ability to treat less susceptible organisms), a longer serum half-life that allows for less frequent dosing, and better taste and tolerability for young children.

No oral cephalosporin at doses studied in children provides activity at the site of infection that equals high-dose amoxicillin. Most second- or third-generation oral cephalosporins provide adequate activity against only 60%–70% of currently isolated strains of pneumococcus. Clindamycin provides in vitro activity against 60%–85% of pneumococci in certain geographic regions, whereas oral levofloxacin or linezolid provide activity against >95% of strains. Daily intramuscular injections of ceftriaxone can be used for outpatient therapy, with in vitro activity documented against >95% of pneumococci [195], with step-down oral therapy after the child has demonstrated a clinical response to parenteral therapy.

Significant macrolide resistance exists in currently isolated strains of *S. pneumoniae*; therefore, currently available macrolides (erythromycin, azithromycin, clarithromycin) are not recommended as empiric therapy when pneumococcal CAP is suspected. Furthermore, azithromycin, with a prolonged serum elimination half-life and prolonged exposure to organisms on respiratory tract mucosa, has been associated with the selection of resistant organisms on mucosal surfaces of treated patients and may represent a source of resistant organisms to others in the community [196].

For those children with a history of nonserious allergic reactions to amoxicillin, treatment is not well defined and should be individualized. Options include a trial of amoxicillin under medical observation for the first dose or a trial of an oral cephalosporin that has substantial activity against *S. pneumoniae*, such as cefpodoxime, cefprozil, or cefuroxime [197], also under medical supervision. For more serious allergies, including

a history of anaphylaxis, treatment options include a respiratory fluoroquinolone, such as levofloxacin, linezolid, a macrolide (recognizing that up to 40% of community isolates of *S. pneumoniae* may be resistant to this class of antibiotic), or clindamycin (if susceptible). For those children with bacteremic pneumococcal pneumonia, particular caution should be exercised in selecting alternatives to amoxicillin, given the potential for secondary sites of infection, including meningitis.

For parenteral therapy of inpatients, higher dosages of β-lactams are also used in the treatment of nonsusceptible strains of pneumococcus than those used for treatment of fully susceptible strains. For regions in which high-level penicillin resistance (MIC >8 μg/mL) among invasive strains is substantial (>25%), higher doses of penicillin G (up to 300 000 U/kg/day given every 4 hours) or ampicillin (up to 400 mg/kg/day given every 6 hours) may be used, similar to dosages demonstrated to be safe for the treatment of meningitis. The required dosing interval for penicillin G is more frequent than for ampicillin or other β-lactam agents owing to a serum half-life in infants as short as 30–40 min.

Alternatively, therapy can be provided with ceftriaxone or cefotaxime in standard, nonmeningitis dosages, as has been documented to be effective in adults with CAP caused by strains previously considered resistant to ceftriaxone [198]. Ceftriaxone and cefotaxime are substantially more active in vitro against penicillin-resistant strains than penicillin G. Microbiologic failures of ceftriaxone have not been reported in children for pneumococcal pneumonia for organisms demonstrating a ceftriaxone MIC <4.0 μg/mL; published data in adults support the use of ceftriaxone for organisms with MICs for ceftriaxone of up to 4 μg/mL [198]. Caution should be exercised when treating resistant pneumococci with other parenteral cephalosporins, as few prospectively collected data exist to document efficacy. Although no prospective evaluations of intravenous ampicillin or amoxicillin compared with ceftriaxone have been conducted in children, limited data in adults suggest that intravenous amoxicillin, as amoxicillin clavulanate (not available in the United States), is as effective as ceftriaxone for strains demonstrating an amoxicillin MIC of up to 2 μg/mL [199].

Costs for penicillin and ampicillin are less than for other antimicrobial agents, but utilization of hospital resources and overall costs for administration of agents given every 4–6 hours may be greater than those for agents given once or twice daily. The lower costs of hospital care, however, need to be balanced by the increased possibility of alteration of the normal microbiome and the emergence of resistance that may occur with any agent that has greater broad-spectrum activity than penicillin G. For children initially treated with broad-spectrum antimicrobials but in whom adequate cultures are either not obtained or are obtained after antimicrobial treatment has begun and do not document a pathogen, transition to oral therapy with amoxicillin is still appropriate.

With respect to the decision regarding the selection of parenteral versus oral empiric therapy of CAP, few prospective data exist to specifically address this issue. Before widespread use of the pneumococcal conjugate vaccine, a retrospective review of children with pneumococcal bacteremia documented that among 61 children with pneumonia, those receiving initial parenteral antibiotic therapy in the emergency department before discharge were more likely to have clinical improvement, including lower magnitude of fever, and less likely to require subsequent hospitalization than those receiving only oral antibiotic therapy [200]. The relevance of this finding to current management is unclear, particularly with widespread use of pneumococcal conjugate vaccines, but the finding suggests that parenteral therapy may be associated with a more rapid response.

Haemophilus influenzae

Universal recommendation of *H. influenzae* type b conjugate vaccine for the past 25 years has virtually eliminated this pathogen in children. Therefore, it is not considered a routine pathogen in CAP. Nontypeable *H. influenzae* is not usually considered a pathogen in pediatric pneumonia except in chronic lung disease or if chronic obstruction develops. When it is isolated and thought to be a true pathogen in pediatric CAP, oral amoxicillin should be effective therapy for mild to moderate infections caused by β-lactamase–negative strains. For β-lactamase–producing organisms causing LRTI, amoxicillin clavulanate or second-generation (cefuroxime), or third-generation (cefdinir, cefixime, cefpodoxime, or ceftibuten) oral cephalosporins should all be effective therapy. Fluoroquinolones are usually not needed for treatment of *H. influenzae* infection in children, except in those who are severely allergic to all oral β-lactam agents. For inpatient therapy, ampicillin is active against virtually all β-lactamase–negative strains in North America, whereas second-generation (cefuroxime) or third-generation (ceftriaxone, cefotaxime) cephalosporins are active against both β-lactamase–negative and –positive strains.

Group A *Streptococcus*

Streptococcus pyogenes (group A streptococcus) remains an infrequent cause of pediatric CAP but may cause severe necrotizing pneumonia. Penicillin or cephalosporin resistance has not been described in this pathogen. Clindamycin resistance is rare and in most geographic areas is <2%. For inpatients, penicillin G may be used to treat disease at a dosage of 100 000–200 000 U/kg/day in 4–6 divided doses, although dosages as high as 200 000–250 000 U/kg/day are well-tolerated and may be used for more severe disease. Macrolides are not considered antimicrobials of choice for treatment of streptococcal infections, because compared with β-lactams, antibiotic resistance for all macrolides is greater, and for erythromycin, tissue concentrations and tolerability are lower. For children with manifestations of toxin-mediated disease (toxic shock–like syndrome), some experts recommend combination therapy with a β-lactam

and clindamycin to decrease the severity of symptoms believed to be caused by streptococcal toxins [201].

Staphylococcus aureus

Pneumonia suspected to be caused by *S. aureus* is most often treated initially in the inpatient setting. Multiple strains or clones of *S. aureus* with differing susceptibility patterns currently circulate in the United States. For inpatients with infection caused by methicillin-susceptible *S. aureus* (MSSA), single drug intravenous therapy with a β-lactamase–stable penicillin (oxacillin or nafcillin) or a first-generation cephalosporin (cefazolin) should be adequate. Combination therapy with an aminoglycoside (gentamicin) is not well studied, although for more severe infections, the combination is used by some experts, particularly for the first days of therapy until a clinical response is achieved. Similarly, combination therapy with a β-lactam and rifampin, supported in part by in vitro data for many, but not all, strains [202], may be used for more severe infections. However, as with aminoglycosides, no prospectively collected, well-controlled clinical data exist for combination therapy with rifampin.

CA-MRSA is an increasing problem in many areas of the United States and comprises >50%–70% of clinical isolates in some regions [203, 204]. Virtually all strains of CA-MRSA isolated from children are susceptible to vancomycin, a bactericidal agent, which is considered the drug of choice for serious infections. Intravenous clindamycin is an alternative agent for both MSSA and MRSA for susceptible strains. Knowledge of local resistance rates and laboratory documentation of susceptibility should guide therapy of serious infections. Inducible resistance to clindamycin may be present in staphylococci (ie, they may be D-test positive); for these strains, clindamycin should not be used in high-inoculum infections such as empyema, for which the risk of the presence organisms that constitutively produce methylase is high. Some experts use clindamycin or other ribosomal-targeted antibiotics when manifestations of toxin-mediated infection are present, but no data from prospective, controlled studies have been collected to date [201]. Some experts use gentamicin, clindamycin, or rifampin in combination with vancomycin for treatment of life-threatening infections caused by CA-MRSA, although no prospectively collected data exist to support this practice. Virtually all strains of CA-MRSA are also susceptible to linezolid, a bacteriostatic agent currently considered second-line therapy. Linezolid may be advantageous if the patient has preexisting renal dysfunction or is receiving other nephrotoxic agents. Daptomycin is inactivated by pulmonary surfactant and is not indicated for the treatment of staphylococcal pneumonia, despite a laboratory report that may document susceptibility.

Children with severe type 1 hypersensitivity to β-lactam drugs who do not tolerate vancomycin or clindamycin can be treated with linezolid, although this antibiotic has a relatively high adverse effect profile. Platelet and neutrophil suppression, and peripheral nerve injury occur more frequently than documented for β-lactam antibiotics, although most adverse effects do not occur until the end of the second week of therapy.

Atypical Pneumonia

Mycoplasma pneumoniae

Symptomatic LRTI has been associated with this pathogen, best described in school-aged children and adults. However, no prospective, randomized, blinded, placebo-controlled clinical trials have been performed specifically for *Mycoplasma* LRTI in children. Most studies of CAP in children that collected information on *Mycoplasma* were retrospective or were prospective but enrolled insufficient numbers of children with infection documented to be caused by *Mycoplasma* to allow statistically valid conclusions regarding the benefit of antibiotics [205]. The recent emergence of macrolide-resistant *M. pneumoniae* in Japan provided an opportunity to compare clinical outcomes in children treated with macrolides who were noted, retrospectively, to be infected with either macrolide-susceptible (MS) strains (n = 47; mean age, 7.5 years) or macrolide-resistant (MR) strains (n = 22; mean age 7.7 years) based on organisms that were cultured and assessed for resistance by both microdilution techniques and PCR identification of mutations previously linked to macrolide resistance. In this retrospective analysis, comparing children infected with MS versus MR strains, days of fever (1.5 vs 4.0 days) and cough (7.0 vs 11.4 days) were both significantly decreased in those infected with MS strains ($P < .01$) [206].

Data extrapolated from adult studies suggests a modest benefit of therapy with tetracyclines and macrolides for illness of mild to moderate severity [207, 208]. It is likely that children with moderate to severe disease will benefit from treatment with macrolides or tetracyclines (for children >7 years). Therapy with the respiratory fluoroquinolones has demonstrated treatment outcomes for adults that are not inferior to macrolides and tetracyclines [27, 209]. Of note, for preschool children with *Mycoplasma* LRTI documented serologically, amoxicillin clavulanate demonstrated clinical outcomes equivalent to those for levofloxacin when evaluated for the primary end point of clinical cure at the test-of-cure visit, 10–17 days after the last dose of the study drug. These results suggest a high rate of spontaneous clinical resolution in *Mycoplasma* infection without need for antimicrobial therapy in this younger age group, although lack of benefit may have resulted from analysis at the test-of-cure visit, without an additional analysis for benefit at much earlier time points into therapy [210].

Chlamydia trachomatis and *C. pneumoniae*

Chlamydia trachomatis is most often identified as a cause of afebrile LRTI in very young infants 2–12 weeks of age, born to mothers with genital infection, whereas *C. pneumoniae* is believed to cause atypical pneumonia in school-aged children and

adolescents [211]. Antimicrobial treatment effects in *C. pneumoniae* LRTI in older children have been difficult to define. Serologic methods of diagnosis have not been well standardized, and a correlation between culture positivity and serologic positivity has been poor [212]. For children with cultures who are treated with macrolides, eradication rates are 70%–80%, but similar rates of clinical improvement occurred in those who were persistently culture positive and in those demonstrating an apparent microbiologic cure [118, 120].

Viral Pathogens in CAP

Influenza

Antiviral therapy exists for susceptible strains of influenza A with adamantanes and neuraminidase inhibitors and for susceptible strains of influenza B with neuraminidase inhibitors. Because substantial genetic variation occurs in influenza from year to year, resistance of influenza virus strains to either class of antiviral agents may develop and spread quickly. The majority of strains of influenza A virus isolated since the 2005–2006 season have been adamantine resistant; resistance to adamantanes is intrinsic to all influenza B strains. The WHO and CDC track and report resistance as strains are analyzed during the influenza season. Dosages of antiviral agents that are currently recommended for seasonal influenza were developed for fully susceptible strains and were evaluated in clinical trials that mandated treatment within 48 hours of onset of symptoms. Although earlier treatment will result in the most benefit [213], patients with serious illness or those with ongoing clinical deterioration after 48 hours of symptoms are still likely to benefit from therapy [214–217]. The degree of benefit has not been defined in these situations.

The optimal dose of oseltamivir is not known for patients with severe illness, those with highly pathogenic avian influenza A (H5N1) infection, those receiving extracorporeal membrane oxygenation [218] or for those with severe immune deficiency, such as transplant recipients. Some experts have suggested higher doses (eg, 150 mg administered orally every 12 hours for persons >40 kg). However, no prospectively controlled data exist on which to base higher dosages or a duration of therapy beyond the standard 5-day treatment course. Investigational neuroaminidase inhibitors that can be administered intravenously were available for treatment of documented H1N1 infections during the H1N1 pandemic, but adequate data on the safety and efficacy of these antiviral agents, particularly for children, are not yet available. More complete information on antiviral therapy is available in the IDSA Guidelines for Influenza [219].

As noted throughout these guidelines, bacterial-viral coinfections have been well-documented to occur with influenza virus, most often documented for *S. pneumoniae, S. aureus* (both methicillin-susceptible and methicillin-resistant strains) and group A streptococcus. Investigation of bacterial infection may still be important in a child with a serious viral LRTI, and empiric therapy for bacterial agents may also be necessary.

Respiratory Syncytial Virus

Controversy exists regarding the efficacy of inhaled ribavirin for treatment of RSV CAP in infants. Ribavirin has in vitro activity against RSV, but use of this drug for RSV infection is not routinely recommended in the management of lower respiratory tract disease owing to considerations of cost, aerosol administration, potential toxic effects among exposed healthcare providers, and efficacy. Effective prophylaxis for RSV infection is available in palivizumab (Synagis), a humanized murine monoclonal antibody administered intramuscularly. Recommendations for target populations for prophylaxis, dosage, and duration of prophylaxis are available through the AAP [220]. Investigational monoclonal antibodies against RSV that are more potent than palivizumab have shown promise in the prophylaxis of RSV infection [221].

Parainfluenza Virus, Adenovirus, Metapneumovirus, Rhinovirus, Coronavirus, and Bocavirus

There no data from prospective, controlled studies for antiviral therapy against these viruses that are associated with pediatric CAP.

VI. How Can Resistance to Antimicrobials Be Minimized?

Recommendations

50. Antibiotic exposure selects for antibiotic resistance; therefore, limiting exposure to any antibiotic, whenever possible, is preferred. *(strong recommendation; moderate-quality evidence)*

51. Limiting the spectrum of activity of antimicrobials to that specifically required to treat the identified pathogen is preferred. *(strong recommendation; low-quality evidence)*

52. Using the proper dosage of antimicrobial to be able to achieve a minimal effective concentration at the site of infection is important to decrease the development of resistance. *(strong recommendation; low-quality evidence)*

53. Treatment for the shortest effective duration will minimize exposure of both pathogens and normal microbiota to antimicrobials, and minimize the selection for resistance. *(strong recommendation; low-quality evidence)*

Evidence Summary

Evidence to support the impact of decreased antibiotic use on the emergence of multidrug resistant organisms in hospitals is available from a number of recent reviews of antimicrobial stewardship programs [215–219]. Although many inpatient programs have demonstrated that antibiotic use can be decreased, few have shown that decreased use of a specific antibiotic can lead to a decrease in the isolation of organisms resistant to that particular antibiotic in the institution. Furthermore, most of the analyses have not assessed the reduction in the actual number of patient infections caused by organisms resistant to a specific

antibiotic, after a reduction in the use of that specific antibiotic. Even fewer high-quality data are available for pediatric infections treated on an outpatient basis [222]. Evidence to support the use of the lowest effective antimicrobial drug exposure (dose and duration) required to prevent the emergence of resistance and subsequent infection by antibiotic resistant organisms has not yet been evaluated and published.

VII. What Is the Appropriate Duration of Antimicrobial Therapy for CAP?

Recommendations

54. Treatment courses of 10 days have been best studied, although shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis. *(strong recommendation; moderate-quality evidence)*

55. Infections caused by certain pathogens, notably CA-MRSA, may require longer treatment than those caused by *S. pneumoniae*. *(strong recommendation; moderate-quality evidence)*

Evidence Summary

The duration of antimicrobial therapy in children in the developed world has primarily been studied in the context of antibiotic registration trials, comparing newer agents with those having a standard treatment course of 10 days (5 days for azithromycin, which has distinctly different tissue-site pharmacokinetics compared with β-lactam antibiotics) in these protocols [13]. Short-course (3-day) therapy has been studied in the developing world, but the clinical, laboratory, and radiographic description of these study patients is less definitive than in developed countries, and documentation of a bacterial pathogen is infrequent [223]. Similar prospective, comparative studies of short-course therapy with intensive investigation for etiology of pneumonia have not been performed in the developed world. Although the total course of therapy is often 10 days, transition to oral therapy has been often used to allow discharge from an inpatient setting, providing decreased risks from intravenous administration of therapy and exposure to nosocomial pathogens. Although no data from prospective, controlled studies are available, retrospective reviews suggest that this practice is effective. Transition from intravenous to daily intramuscular therapy with long-acting antibiotics, particularly β-lactams such as ceftriaxone or ertapenem, may provide another option for hospital discharge for the child who no longer requires supplemental oxygen and skilled nursing care but may still require parenteral therapy. In areas with skilled pediatric outpatient nursing resources, for children who may require longer duration of parenteral therapy, outpatient intravenous therapy through an indwelling central catheter, with daily skilled pediatric home nursing visits, provides another option for out-of-hospital care [224].

The duration of parenteral therapy before transition to oral therapy is based on the severity of the initial presentation and the rapidity of improvement. Improvement in fever, cough, tachypnea, and supplemental oxygen dependency and increased activity and appetite, supported by a reduction in peripheral leukocyte counts and/or CRP or other acute-phase reactants, are used by many clinicians to aid in decisions regarding transition to oral therapy. In the absence of bacteremia, or in children with bacteremia in whom secondary foci of infection have not been found, transition to oral therapy can take place as early as 2–3 days after the start of parenteral therapy, although data to support this recommendation are primarily retrospective [225].

In addition to amoxicillin, other oral antibiotic options are available for the allergic child, depending on the antimicrobial susceptibility of the pathogen. Certain antimicrobial drugs demonstrate excellent absorption from the gastrointestinal tract and, if deemed to be appropriate therapy, are likely to be as effective by mouth as by parenteral route for the convalescing child in a compliant family. Such antimicrobials include fluoroquinolones, linezolid, clindamycin, trimethoprim-sulfamethoxazole, and azithromycin.

Infections caused by certain pathogens, notably CA-MRSA, may require longer treatment than those caused by *S. pneumoniae* [226]. Complicated infections that result in parapneumonic effusions, empyema, or lung abscess may also require therapy for >10 days, but prospective, randomized trials that define duration based on attributes of the pathogen and the characteristics of the pneumonia have not been performed. Some experts would treat an appropriately drained effusion or empyema 7–10 days after resolution of fever, whereas others recommend therapy for up to 4–6 weeks. Lung abscesses are varied in size and microbial etiology; therapy should be individualized based on the clinical, laboratory, and imaging response to antimicrobial treatment.

VIII. How Should the Clinician Follow the Child With CAP for the Expected Response to Therapy?

Recommendation

56. Children receiving adequate therapy should demonstrate clinical and laboratory signs of improvement within 48–72 hours. For children whose condition deteriorates after admission and initiation of antimicrobial therapy or who show no improvement within 48–72 hours, further investigation should be performed. *(strong recommendation; moderate-quality evidence)*

Evidence Summary

Clinical signs and symptoms, including fever, respiratory rate, and oxygenation (as measured by pulse oximetry and supplemental oxygen requirement), should demonstrate improvement within 48–72 hours, based on data originally collected >50 years ago in placebo-controlled trials when antimicrobial therapy first became available [227]. Clinical findings of response to therapy may be

supported by laboratory markers of inflammation (certain acute-phase reactants such as procalcitonin or CRP), although these laboratory tests have not been routinely incorporated into clinical trial design and have not been adequately evaluated or validated [228]. Further discussion on management of these children is provided in the Evidence Summary for Recommendation 71.

ADJUNCTIVE SURGICAL AND NON–ANTI-INFECTIVE THERAPY FOR PEDIATRIC CAP

IX. How Should a Parapneumonic Effusion Be Identified?

Recommendation

57. History and physical examination findings may be suggestive of parapneumonic effusion in children suspected of having CAP, but chest radiography should be used to confirm the presence of pleural fluid. If the chest radiograph is not conclusive, then further imaging with chest ultrasound or CT is recommended. *(strong recommendation; high-quality evidence)*

Evidence Summary

Parapneumonic effusion is defined as a collection of fluid in the pleural space associated with underlying pneumonia. In a large study of patients with CAP in Canada, parapneumonic effusions were observed in ~9% of adult patients [229]. In children, prospective studies of CAP in Europe and the Americas have demonstrated parapneumonic effusions in 2%–12% [230–233]. Parapneumonic effusions may occur in up to 20% of pneumonias due to *M. pneumoniae* and may also be seen in ~10% of viral pneumonias [17, 234], but these effusions are rarely large enough to require intervention. Parapneumonic effusions occur most frequently with bacterial pneumonia, occurring in ~50% of cases due to typical bacteria including *S. pneumoniae, S. pyogenes,* and *S. aureus* in countries where *H. influenzae* type b vaccine is in general use [17].

Parapneumonic empyema is a collection of pus in the pleural space associated with an underlying pneumonia. Pus may be defined by gross appearance, WBC count (>50 000 WBCs/μL) [235], or positive bacterial culture. Hospitalization rates for parapneumonic empyema are increasing in the United States [45, 89, 236–238].

In children with CAP, parapneumonic effusion may be suspected based on history and physical examination. In children with CAP, prolonged fever, chest pain, and abdominal pain have all been associated with parapneumonic effusion [89, 239]. Physical examination may reveal signs of pleural fluid, including dullness to percussion, diminished breath sounds, and a change in the quality of breath sounds and transmitted speech over the effusion. Chest radiography, including lateral decubitus views, should be used to confirm the presence of pleural fluid in children with CAP. If there is still a question of pleural fluid versus parenchymal opacification, then further imaging with chest ultrasound or CT scan is warranted. Chest ultrasound is considered a safer imaging procedure than CT, owing to lack of ionizing radiation.

X. What Factors Are Important in Determining Whether Drainage of the Parapneumonic Effusion Is Required?

Recommendations

58. The size of the effusion is an important factor that determines management (Table 8, Figure 1). *(strong recommendation; moderate-quality evidence)*.

59. The child's degree of respiratory compromise is an important factor that determines management of parapneumonic effusions (Table 8, Figure 1) *(strong recommendation; moderate-quality evidence)*.

Evidence Summary Drainage of a parapneumonic effusion may be required for several reasons. The most common cause of parapneumonic effusion in children is infection. If there is doubt about the infectious etiology of the effusion or if malignancy is suspected, thoracentesis may be performed for cytologic examination. When an empyema is present, drainage of purulent material is usually required for adequate treatment of the infection. Drainage of infected pleural fluid may result in decreased fever, inflammation, and hospital stay [240, 241]. Finally, the size of the effusion and the degree of respiratory compromise are important factors to be considered when determining the management plan. Small effusions (see Table 8) often respond well to antibiotic therapy and usually require no further intervention. Moderate to large effusions are more likely to cause respiratory compromise, not resolve quickly and benefit from drainage, as outlined in Figure 1.

Although the classification of effusion size is both qualitative and arbitrary, the effusion size classification criteria used in this guideline are similar to those recommended for adult patients [242, 243], and they have also been used in at least 2 recent investigations [244, 245]. Small effusions (<10 mm rim of fluid on lateral decubitus or less than one-fourth of the hemithorax opacified on an upright chest radiograph) are likely to resolve on their own and usually do not require drainage. Reporting their 12-year, single-institution, retrospective experience with pneumonia and parapneumonic effusions, Carter et al noted that no small pleural effusion required drainage; all patients with small effusions recovered uneventfully with antibiotic therapy alone [245]. In the absence of mediastinal shift, only 27% of patients (23 of 84) with moderate pleural effusions required drainage. Carter et al also noted that of 94 children with large effusions (more than half of the hemithorax opacified), 62 (66%) ultimately required pleural drainage. In adults, Ferguson et al noted that simple aspiration and drainage were likely to fail in

effusions occupying >40% of the hemithorax [246]. This was also the consensus in the British Thoracic Society guidelines for children [241] and the adult-based American College of Chest Physicians consensus statement [243]. There are few data concerning moderate effusions, although Carter et al noted that the majority of children with moderate effusions were successfully managed without pleural drainage; only 1 child treated initially with antibiotics alone required readmission for pleural fluid drainage [245]. However, further prospective studies are needed in this area.

In effusions large enough warrant consideration of drainage, the presence of loculated or ''organizing'' fluid influences treatment decisions, because drainage by chest thoracostomy tube alone may not be effective and adjunctive therapy may be required. The choice of adjunctive therapy is discussed below. The imaging study of choice to assess for pleural fluid loculations is chest ultrasound, although lateral decubitus radiography and CT of the chest can also be used. There is some evidence that loculated parapneumonic effusions are associated with more complicated hospital courses. Ramnath et al found that children with loculated parapneumonic effusions treated with antibiotics alone, either with or without chest tube placement, had longer lengths of stay and more complicated courses than those with simple (nonloculated) effusions that were treated similarly [247]. Himelman et al noted that adults with loculated parapneumonic effusions had larger effusions and longer hospital stays and underwent thoracostomy procedures more frequently than those with nonloculated effusions [248]. However, Carter et al found that pleural fluid loculations were not associated with the need for pleural drainage [245].

XI. What Laboratory Testing Should Be Performed on Pleural Fluid?

Recommendation

60. Gram stain and bacterial culture of pleural fluid should be performed whenever a pleural fluid specimen is obtained. *(strong recommendation; high-quality evidence)*

61. Antigen testing or nucleic acid amplification through PCR increase the detection of pathogens in pleural fluid and may be useful for management. (*strong recommendation; moderate-quality evidence*)

62. Analysis of pleural fluid parameters, such as pH, glucose, protein, and lactate dehydrogenase, rarely changes patient management and is not recommended. (*weak recommendation; very weak-quality evidence*)

63. Analysis of the pleural fluid WBC count, with cell differential analysis, is recommended primarily to help differentiate bacterial from mycobacterial, fungal, or malignancy etiologies. *(weak recommendation; moderate-quality evidence)*

Evidence Summary

Gram stain and bacterial culture of pleural fluid are positive in up to 49% of cases of pneumonia complicated by parapneumonic effusion, with most investigators reporting positive cultures in <25% [89, 249–254]. When positive, pleural fluid culture can direct antibiotic therapy. Unfortunately, the majority of parapneumonic effusions, although thought to be caused by pathogenic bacteria, are culture negative. Using nucleic acid or antigen detection methods, several studies in the United States and Europe have demonstrated that culture-negative empyema is caused primarily by *S. pneumoniae,* often nonvaccine serotypes that are susceptible to penicillin [226, 249, 250, 255–258]. These methods have greater sensitivity than traditional culture-based methods, identifying bacterial pathogens in 42%–80% of samples, especially in patients pretreated with antibiotics [226, 259, 260] Antigen and nucleic acid assays for the diagnosis of pathogens responsible for parapneumonic empyema, including *S. pneumoniae* and *S. aureus*, are still in development, but these tests may be helpful in centers where they are available. Most of these tests are not currently FDA-approved, but many developers may not wish to seek full FDA approval for use in neonates, infants and children based on economic, medical and ethical concerns.

Biochemical tests of pleural fluid are often performed in adults to distinguish exudative from transudative effusions and to help guide clinical management [235]. In children, the overwhelming majority of parapneumonic effusions are due to infection. Biochemical tests are rarely required to help establish the etiology (eg, infection vs malignancy or other cause) of the effusion and have rarely been associated with changes in patient management. In adult patients, a meta-analysis demonstrated that pH had the highest diagnostic accuracy for identifying complicated parapneumonic effusions requiring pleural fluid drainage with an area under the receiver operating characteristic (ROC) curve of 0.92, compared with 0.84 for pleural fluid glucose and 0.82 for lactate dehydrogenase. Even after exclusion of pleural fluid that was grossly purulent, pH retained a high diagnostic accuracy (area under the ROC curve, 0.89) with decision thresholds at pH cutoff values between 7.21–7.29 [261]. In children, pH values <7.2 have been associated with need for pleural fluid drainage [262]. Biochemical testing of pleural fluid in children with parapneumonic effusions associated with pneumonia is not required. However, some experts believe that measurement of pleural fluid pH, obtained at the time of initial drainage, may help guide decisions regarding need for pleural fluid drainage.

WBC counts with differential analysis have been conventionally been performed in pleural fluid, but the value of this analysis in demonstrating bacterial etiology is being replaced by molecular analysis. The value of the pleural fluid cell count in

Table 9. Summary of Published Fibrinolysis Regimens

Published source, year	Fibrinolytic agent	Concentration	Regimen	Total no. of doses
St Peter et al, 2009 [92]	Tissue plasminogen activator	4 mg mixed in 40 mL of normal saline	First dose at time of chest tube placement with 1-hour dwell time,[a] after which chest tube is placed on continuous suction (–20 cm H_2O); repeat every 24 hours	3
Hawkins et al, 2004 [266]	Tissue plasminogen activator	0.1 mg/kg with a maximum of 3 mg mixed in 10–30 mL of normal saline	First dose after placement of pigtail catheter with 45–60-minute dwell time,[a] after which chest tube is placed on continuous suction (–20 to –25 cm H_2O); repeat every 8 hours	9
Sonnappa et al, 2006 [267]	Urokinase	10 000 U in 10 mL of normal saline for children <1 year old; 40 000 U in 40 mL of normal saline for children >1 year old	First dose at placement of chest tube with 4-hour dwell time,[a] after which chest tube is placed on continuous suction (–10 to –20 cm H_2O); repeat every 12 hours	6

[a] Chest drain remains clamped during ''dwell time.''

predicting morbidity and outcome does not justify a strong recommendation [263]. However, clues to the origin of pleural fluid caused by less common etiologies, such as tuberculosis and malignancy, may be found in the cell count, differential analysis, and cytologic findings for the fluid [264, 265].

XII. What Are the Drainage Options for Parapneumonic Effusions?

Recommendations

64. Small, uncomplicated parapneumonic effusions should not routinely be drained and can be treated with antibiotic therapy alone. *(strong recommendation: moderate-quality evidence)*

65. Moderate parapneumonic effusions associated with respiratory distress, large parapneumonic effusions, or documented purulent effusions should be drained. *(strong recommendation; moderate-quality evidence)*

66. Both chest thoracostomy tube drainage with the addition of fibrinolytic agents and VATS have been demonstrated to be effective methods of treatment. The choice of drainage procedure depends on local expertise. Both of these methods are associated with decreased morbidity rates compared with chest tube drainage alone. However, in patients with moderate to large effusions that are free flowing (no loculations), placement of a chest tube without fibrinolytic agents is a reasonable first option. *(strong recommendation; high-quality evidence)*

Evidence Summary

The choice of drainage procedure depends on local or regional expertise and experience. In patients with pleural fluid that is not loculated, initial drainage with a chest tube alone is an option, though proceeding directly to adjunctive therapy is also reasonable. Loculated effusions cannot be drained with a chest tube alone and thus require adjunctive therapy. Both chest tube drainage with the instillation of fibrinolytic agents, including urokinase or tissue plasminogen activator, and VATS have been advocated as effective treatment measures for pediatric parapneumonic effusions [92, 266–269]. Either chest tube drainage with fibrinolysis or VATS is preferred (over chest tube drainage alone) for complicated, loculated effusions; currently available data are not adequate to determine that one procedure is clearly preferred over the other. See Table 9 for fibrinolytic regimens used with children [92, 266, 267]. Both interventions have been reported to have improved patient outcomes, including resolution of infection and decreased length of hospital stay, when compared with conservative treatment with chest tube drainage and antibiotics [92, 266–268, 270]. Two single-center randomized controlled trials compared fibrinolytic therapy with VATS. Although different strategies for fibrinolysis were used by Sonnappa et al (30 patients treated with urokinase, 30 with VATS) and St Peter et al (18 patients treated with alteplase, 18 treated with VATS), both studies demonstrated similar patient outcomes, including length of hospital stay, and both also demonstrated a decreased cost for treatment of parapneumonic empyema with fibrinolytic agents compared with VATS [92, 267]. A randomized trial by Kurt et al (10 patients treated with VATS, 8 treated with conventional tube thoracostomy with reteplase fibrinolysis solely as rescue therapy) documented shorter length of stay among patients undergoing initial VATS [271]. Based on the currently available data, both chest tube with fibrinolysis and VATS are considered acceptable initial drainage strategies.

XIII. When Should VATS or Open Decortication Be Considered in Patients Who Have Had Chest Tube Drainage With or Without Fibrinolytic Therapy?

Recommendation

67. VATS should be performed when there is persistence of moderate to large effusions and ongoing respiratory compromise, despite ~2–3 days of management with a chest

tube and completion of fibrinolytic therapy. Open chest débridement with decortication represents another option for management of these children but is associated with higher morbidity rates. *(strong recommendation; low-quality evidence)*

Evidence Summary

Approximately 17% [92, 266, 267] of children with parapneumonic effusions treated with fibrinolytic agents via a chest tube will require further intervention to complete drainage of the pleural space. Children who require further intervention with VATS or open thoracotomy or decortication are those who have persistence of moderate or large effusions and ongoing respiratory compromise despite ~2–3 days of management with a chest tube and fibrinolytic agents. Persistence of fever alone is not an indication of treatment failure. Chest CT should be performed to evaluate the adequacy of pleural fluid drainage and to determine whether loculated fluid collections or necrotizing parenchymal disease are present. After failure of chest tube with fibrinolytic agents, drainage of the pleural space is most often accomplished by VATS; rarely, children will require open decortication. It is not routinely necessary to obtain chest radiographs serially after VATS or chest tube placement.

XIV. When Should a Chest Tube Be Removed After Either Primary Drainage or VATS?

68. A chest tube can be removed in the absence of an intrathoracic air leak and when pleural fluid drainage is <1 ml/kg/24 h, usually calculated over the last 12 hours. *(strong recommendation; very low-quality evidence)*

Evidence Summary

Once a chest tube is placed, either as primary treatment or after VATS, criteria for removal include the absence of an air leak and <1 mL/kg/24 h of pleural fluid drainage, usually calculated over the last 12 hours, or ~25–60 mL total in a 24-hour period [92, 266, 267]. This can often be accomplished within 48–72 hours after the operation or completion of fibrinolysis.

XV. What Antibiotic Therapy and Duration Is Indicated for the Treatment of Parapneumonic Effusion or Empyema?

Recommendations

69. When the blood or pleural fluid bacterial culture identifies a pathogenic isolate, antibiotic susceptibility should be used to determine the antibiotic regimen. *(strong recommendation; high-quality evidence)*

70. In the case of culture-negative parapneumonic effusions, antibiotic selection should be based on the treatment recommendations for patients hospitalized with CAP (see Evidence Summary for Recommendations 46–49). *(strong recommendation; moderate-quality evidence)*

71. The duration of antibiotic treatment depends on the adequacy of drainage and on the clinical response demonstrated for each patient. In most children, antibiotic treatment for 2–4 weeks is adequate *(strong recommendation; low-quality evidence)*.

Evidence Summary

The antibiotic treatment of parapneumonic effusion or empyema is similar to that for CAP without effusion. The bacterial pathogens responsible for CAP and for parapneumonic effusion or empyema are also similar, with *S. pneumoniae* the most commonly isolated pathogen in most studies [236, 237, 242–246], though *S. aureus* remains an important cause of empyema but a less common cause of uncomplicated CAP. Whenever possible, antibiotic therapy should be pathogen directed, based on results of bacterial culture of either blood or pleural fluid. Unfortunately, pleural fluid cultures are often negative owing to the high frequency of antibiotic treatment initiated before fluid is obtained for culture. In these circumstances, treatment is based on regional epidemiology and selected to provide coverage for the most common pathogens (see Evidence Summary for Recommendations 46–49). When molecular testing is used, culture-negative empyema is most often found to be due to *S. pneumoniae* that had been partially treated before bacterial cultures were obtained and has rarely been found to be due to *S. aureus* [226, 250, 256–258]. Empyema caused by *S. aureus,* especially CA-MRSA, results in positive bacterial culture more often than empyema caused by pneumococcus. In a single-center study of 63 pleural fluid specimens tested by bacterial culture and PCR, all cases of CA-MRSA were demonstrated by both culture and PCR. No cases of MRSA were demonstrated by PCR in culture negative pleural fluid [226], although this finding should be verified in settings with higher incidences of CA-MRSA.

The optimal duration of antibiotic treatment for parapneumonic effusion or empyema is dependent on the adequacy of the drainage procedure and may vary by pathogen, but it has not been determined through randomized controlled trials. Treatment for 2–4 weeks is commonly recommended; some experts treat the infection for ~10 days after resolution of fever.

MANAGEMENT OF THE CHILD NOT RESPONDING TO TREATMENT

XVI. What Is the Appropriate Management of a Child Who Is Not Responding to Treatment for CAP?

Recommendation

72. Children who are not responding to initial therapy after 48–72 hours should be managed by one or more of the following:

a. Clinical and laboratory assessment to determine the current severity of their illnesses and anticipated progression in order

to determine whether higher levels of care or support are required. *(strong recommendation; low-quality evidence)*

b. Imaging evaluation to assess the extent and progression of the pneumonic or parapneumonic process. *(weak recommendation; low-quality evidence)*

c. Further investigation to identify whether the original pathogen persists, whether it has developed resistance to the agent used, or whether there is a new secondary infecting agent. *(weak recommendation; low-quality evidence)*

73. A BAL (BAL) specimen should be obtained for Gram stain and culture for the mechanically ventilated child. *(strong recommendation; moderate-quality evidence)*

74. A percutaneous lung aspirate should be obtained for Gram stain and culture in the persistently and seriously ill child for whom previous investigations have not yielded a microbiologic diagnosis. *(weak recommendation; low-quality evidence)*

75. An open lung biopsy for Gram stain and culture should be obtained in the persistently and critically ill, mechanically ventilated child for whom previous investigations have not yielded a microbiologic diagnosis. *(weak recommendation; low-quality evidence)*

Evidence Summary

The decision to consider a patient as a nonresponder during therapy for bacterial or viral CAP is based on the clinician's interpretation of the patient's clinical course and, at times, laboratory data relative to the patient's condition at the onset of therapy. In general, the clinician should consider a patient a nonresponder if there is a lack of improvement within 48–72 hours or significant worsening at any time after initiation of therapy.

The frequency of nonresponse in pediatric pneumonia is not well described but has been estimated overall at between ~5% and 15% in hospitalized children [272]. This is similar to findings of a meta-analysis of prospective randomized trials in adults investigating treatment failure, in which persistent fever and deterioration of the patient's condition requiring a change in prescribed antibiotics was seen in 16% of patients [273].

Clinical judgment is paramount in defining nonresponse, but the determination of nonresponse is also influenced by laboratory and/or imaging results. The relative weights of these factors in the decision to consider a patient a nonresponder vary by age, the setting (outpatient vs inpatient vs ICU), the severity of the presentation, and finally the rate of clinical deterioration or duration of the lack of improvement.

The following factors influence the decision to consider the patient a nonresponder at 48–72 hours:

A. Vital signs and oxygen saturation [45]

1. Persistence or increase in the general fever pattern

2. Increased respiratory rate, grunting, chest retractions, cyanosis

3. Persisting increased heart rate

4. Oxygen saturation <90% with room air, need for supplemental oxygen or ventilation

B. Systemic or focal symptoms or signs

1. Clinically defined "toxicity" based on clinical judgment or change in mental status 2. Chest pain, splinting of the chest

3. Inability to maintain oral intake and hydration

4. Extent of abnormal or absent breath sounds at auscultation or dullness in response to percussion

C. Laboratory and/or radiologic results

1. Peripheral WBC count, taking into account the total count and percentage of immature forms of neutrophils

2. Levels of inflammatory markers (eg, procalcitonin, CRP)

3. Isolation of a pathogen by culture; nonresponsive pathogens include either those with antimicrobial resistance to current therapy or those susceptible to current therapy but with inadequate drug exposure in infected tissues, inadequate drainage of empyema or abscess, or inadequate duration of therapy.

4. Increased degree of parenchymal involvement, presence of or increase in pleural fluid, or development of pulmonary abscess or necrotizing pneumonia, as documented by imaging with chest radiography, ultrasound, or CT.

Children with nonresponding CAP should have the clinical severity of their condition repeatedly assessed to determine whether they require higher levels of care, for example, admission to the hospital from the outpatient setting, skilled transport from a community hospital to a tertiary pediatric care center, or transfer to the ICU from a hospital ward. The evaluation should include monitoring for the expected improvements in presenting findings that may include fever, respiratory rate, respiratory distress (chest retractions, grunting), and hypoxemia (with pulse oximetry). Children should also be monitored for their global response in terms of activity, appetite, and hydration status. Some outpatient "nonresponders" will require hospitalization (see Evidence Summary for Recommendation 1) if they are unable to maintain adequate oxygenation or hydration or show signs of increased work of breathing or toxicity. Children treated initially with oral antibiotic therapy for presumed bacterial or atypical pneumonia as outpatients may actually be infected by pathogens not susceptible to initial therapy, and may require alternative or additional antibacterial or antiviral therapy.

Children with nonresponding CAP that is moderate to severe should undergo radiographic imaging, particularly if clinical evidence suggests increased respiratory effort, increased areas of abnormal lung sounds, or dullness to percussion in areas where it was not detected previously. For outpatients, the preferred imaging study is chest radiography including posteroanterior and

lateral views. If a moderate to large pleural effusion is suspected, then a lateral decubitus chest radiograph or a chest ultrasound is indicated (see Evidence Summary for Recommendation 57). If a chest mass, pulmonary abscess, or necrotizing pneumonia is suspected, chest CT should be performed.

Children with complications of pneumonia, including moderate to large pleural effusions, require consultation with those services in the institution that have expertise in obtaining pleural fluid specimens and providing drainage, fibrinolytic agents, and/or VATS (see Evidence Summary for Recommendations 58 and 59).

Reassessment for bacterial pathogens may include sputum for culture in children who can cough and expectorate. In children with parapneumonic effusions who are not responding to antimicrobial therapy alone, pleural fluid samples should be obtained for culture, Gram stain, and, if available, either PCR [258, 259] or antigen testing [274]; samples should also be evaluated for mycobacteria and fungi with appropriate stains and cultures, in the context of a clinically relevant exposure and clinical presentation. Children should also be considered for drainage or removal of the effusion. In seriously ill children requiring mechanical ventilation, cultures obtained by bronchoscopy using BAL, tracheal aspirate, or bronchial brush may be helpful.

Although rare pathogens can present as CAP, CAP in children is usually caused by the traditional respiratory tract pathogens (see Etiology). When CAP is not responding to initial empiric antimicrobial therapy, particularly if an attempt to discover a pathogen was initially not considered necessary, there should be a more aggressive approach to pathogen identification. Furthermore, the patient should be reassessed to consider whether more resistant common bacterial or viral pathogens or unusual pathogens, including fungal, mycobacterial, or parasitic organisms, may be responsible for worsening signs and symptoms. Secondary bacterial infection from an airway obstructed from either intrinsic or extrinsic mechanisms should also be considered.

Inpatients who fail to respond to initial therapy may require expansion of antimicrobial therapy for pathogens that are not included in the spectrum of the initial antibiotic choice or that subsequently display resistance to the initial agent by means of induction of resistance mechanisms, mutation, or selection of a small subpopulation of the pathogen that is intrinsically resistant to the agent but not detected on initial cultures. For example, a patient initially treated with intravenous ampicillin should have coverage broadened with either nafcillin-oxacillin or cefazolin for MSSA or with clindamycin (moderately ill patients) or vancomycin (patients with severe or life-threatening conditions) for MRSA. Another example is represented by patients receiving long-term treatment with vancomycin for infection caused by CA-MRSA in whom selection for "heteroresistance" to vancomycin occurs, with increasing MICs that require an increasing dosage of vancomycin to achieve cure [275]. Patients who require significant intervention to maintain adequate oxygenation or perfusion, such as mechanical ventilation, cardiovascular support, or extracorporeal membrane oxygenation support, should be transferred to a unit capable of providing intensive care.

When nonresponding CAP is suspected to be either viral in origin or a result of coinfection with bacterial and viral pathogens, confirming a viral pathogen can be beneficial. Rapid antigen testing and PCR have the advantage of rapid turnaround times, but the availability and expense of PCR testing can be a limiting factor. As the accessibility of molecular-based technologies such as PCR increases, and costs decrease, these tests may replace many antigen-based tests, because they generally have improved test performance characteristics and can identify an increasing number of viral pathogens.

A nonresponding child with CAP may have influenza virus infection alone that is resistant to empiric antiviral treatment with oseltamivir. In such patients, testing for oseltamivir resistance should be pursued through public health laboratories, and treatment should be initiated with an alternative antiviral agent, such as zanamivir, or an investigational antiviral agent that may retain activity against the influenza strain. For children <7 years old, or for those who require intravenous antiviral therapy, investigational antiviral therapy may be required, usually through the drug manufacturer. Children with worsening CAP and a viral pathogen should receive antiviral treatment if available and should undergo further testing aimed at identifying previously undetected bacterial pathogens (see Evidence Summary for Recommendations 28, 29, 39, and 40).

Children who present with initially confirmed viral CAP occasionally develop secondary bacterial infection. Secondary bacterial infection in infants and children with viral disease occurs most frequently in hospitalized children, especially those with influenza [276–278] or RSV infection requiring intensive care [117, 279–282]. If secondary bacterial infection is suspected with clinical deterioration supported by laboratory evidence of increased systemic inflammation, then investigation for bacterial pathogens is warranted, and antibacterial therapy should be expanded to provide coverage for common bacterial pathogens, keeping in mind the local resistance patterns. Occasionally, in children $\geq$3–5 years old, testing for *Mycoplasma* or *C. pneumoniae* is warranted, particularly if pulmonary infiltrates are perihilar and bilateral and wheezing is present. If test results require several days, clinicians should start empiric therapy with the addition of a macrolide, tetracycline, or fluoroquinolone (see Evidence Summary for Recommendations 44 and 48).

XVII. How Should Nonresponders With Pulmonary Abscess or Necrotizing Pneumonia Be Managed?

Recommendation

76. A pulmonary abscess or necrotizing pneumonia identified in a nonresponding patient can be initially treated with

intravenous antibiotics. Well-defined peripheral abscesses without connection to the bronchial tree may be drained under imaging-guided procedures either by aspiration or with a drainage catheter that remains in place, but most will drain through the bronchial tree and heal without surgical or invasive intervention. *(weak recommendation; very low-quality evidence)*

Evidence Summary

Most pulmonary abscesses arise in previously normal lung as a result of an initial pneumonia. The abscess and/or lung necrosis may lead to a lack of clinical response. The non-responding patient who has a lesion on chest radiograph suggestive of abscess or necrotizing pneumonia should undergo CT of the chest with contrast medium enhancement to help confirm or rule out these processes. In general, surgical intervention should be avoided, because most abscesses resolve with antibiotics alone [283, 284]. However, if the abscess is peripheral and not associated with airway connection, then CT-guided drainage or catheter placement is a reasonable option [285–287]. Retrospective data suggest that drainage shortens hospital stays and facilitates earlier recovery [288]. Specimens obtained at drainage should be methodically investigated for potential pathogens.

Patients with a secondary abscess due to an underlying pulmonary anomaly or lesion (eg, congenital cystic adenomatoid malformation, pulmonary sequestration) require surgical consultation for evaluation of long-term management of the lesion, and to determine whether surgical resection is required. Necrotizing pneumonia should be treated medically because surgical intervention and/or placement of chest tubes via trocar may increase the risk for bronchopleural fistula [286].

Discharge Criteria

XVIII. When Can a Hospitalized Child With CAP Be Safely Discharged?

Recommendations

77. Patients are eligible for discharge when they have documented overall clinical improvement, including level of activity, appetite, and decreased fever for at least 12–24 hours. *(strong recommendation; very low-quality evidence)*

78. Patients are eligible for discharge when they demonstrate consistent pulse oximetry measurements >90% in room air for at least 12–24 hours. (*strong recommendation; moderate-quality evidence*)

79. Patients are eligible for discharge only if they demonstrate stable and/or baseline mental status. *(strong recommendation; very low-quality evidence)*

80. Patients are not eligible for discharge if they have substantially increased work of breathing or sustained tachypnea or tachycardia (*strong recommendation; high-quality evidence)*

81. 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. *(strong recommendation; low-quality evidence)*

82. For infants or young children requiring outpatient oral antibiotic therapy, clinicians should demonstrate that parents are able to administer and children are able to adequately comply with taking those antibiotics before discharge. *(weak recommendation, very low-quality evidence)*

83. 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, with either no clinical evidence of deterioration since removal, or if a chest radiograph was obtained for clinical concerns, radiographic evidence of no significant reaccumulation of a parapneumonic effusion or pneumothorax. *(strong recommendation; very low-quality evidence)*

84. In infants and children with barriers to care, including concern about careful observation at home, inability to comply with therapy, or inability to be followed up, these issues should be identified and addressed before discharge. *(weak recommendation; very low-quality evidence)*

Evidence Summary

There are no studies that clearly determine the best criteria for hospital discharge. However, the following criteria are commonly used: (1) the child has decreasing fever, (2) no supplemental oxygen is required, (3) the child has been taking foods and liquids adequately for at least 12–24 hours, and (4) if a chest tube was placed, the child is free of intrathoracic air leak for at least 12–24 hours after the tube is removed. In adults, improvement of pneumonia has been primarily determined by improved fever course, resolution of tachycardia and tachypnea, improved systolic blood pressure, and resolution of a need for supplemental oxygen as assessed by pulse oximetry [289]. In children, criteria for stability in the course of treatment of pneumonia are far less well defined.

Fever is extremely common in pneumonia, and may persist for several days despite adequate therapy, particularly for children with complicated pneumonia [290, 291]. In a study of adults, lowering of a threshold of what is considered a "stable" temperature does not alter time to discharge from the hospital, implying that, at least in that group, temperature stability is not the prime consideration for discharge [289]. Because resolution of fever is a sign of adequate therapy for bacterial pneumonia, an improving fever curve can be used to document the adequacy of therapy in the absence of a definitive organism and sensitivities.

There is wide variability in practice among physicians as to what is considered a safe pulse oximetry level for discharged

patients with pneumonia [49]. However, the use of 90% as a cutoff for oxygen supplementation is recommended for viral respiratory illness [292]. As pulse oximetry measurements fall below 90% (acid-base status, temperature, and other considerations notwithstanding), further decreases in oxygenation result in a faster decline in saturation rates, as determined by the oxygen-dissociation curve of hemoglobin.

Infants and children given unpleasant-tasting antibiotics are more likely to spit out their dose [293, 294]. It has been suggested that for infants and children taking liquid medications, taste has more of an impact on adherence with a prescribed therapy than interval or duration of dosing [295]. A trial of oral antimicrobial therapy before discharge is important, particularly for agents such as liquid clindamycin, which is known to have an unpalatable taste. Ways to improve the palatability of certain antibiotic suspensions exist, including both flavorings available in the home and flavorings that can be added at the time the antibiotic is reconstituted in a pharmacy. Close follow-up with the primary care practitioner is important to make sure that the child continues to tolerate oral antimicrobial therapy.

Children with complicated pneumonia often have surgical procedures to drain accumulation of pleural fluid. Up to a third of patients who have primary chest tube placement may require a second surgical procedure for further fluid drainage [270]. Length of stay and likelihood of reaccumulation of fluid will be significantly reduced, but not eliminated, by VATS or fibrinolytic therapy via chest tube [270, 298] (see Evidence Summary for Recommendations 64 and 65). However, care must be taken that patients do not have ongoing accumulation of pleural fluid before discharge, which may necessitate a more conservative approach to discharge criteria. For patients who do not receive fibrinolytic therapy or VATS, a longer period of observation for accumulation may be warranted.

It is prudent to take into consideration both economic and social conditions that will impact compliance with care and safety of discharge in these patients. Although the effect of cost of outpatient medication on adherence has not been studied in pediatric pneumonia, low-income parents are less likely to comply with prescribed medicines for a variety of medical illnesses [297, 298]. For children with pneumonia who are being discharged, it is reasonable to verify that a patient's prescribed regimen as well as follow-up outpatient services and care will not incur a cost that will reduce the likelihood of compliance.

In one large Canadian study, children with pneumonia were more likely to be hospitalized simply because they were of lower socioeconomic status, presumably because of poor timely access to adequate outpatient services [59]. In another study in the United States, children hospitalized with CAP who came from families with incomes below the federal poverty threshhold represented 11% of children whose hospitalizations were considered avoidable [58].

XIX. When Is Parenteral Outpatient Therapy Indicated, in Contrast to Oral Step-Down Therapy?

Recommendations

85. Outpatient parenteral antibiotic therapy should be offered to families of children no longer requiring skilled nursing care in an acute care facility but having a demonstrated need for ongoing parenteral therapy. *(weak recommendation; moderate-quality evidence)*

86. Outpatient parenteral antibiotic therapy should be offered through a skilled pediatric home nursing program or through daily intramuscular injections at an appropriate pediatric outpatient facility. *(weak recommendation; low-quality evidence)*

87. Conversion to oral outpatient step-down therapy, when possible, is preferred to parenteral outpatient therapy. *(strong recommendation; low-quality evidence)*

Evidence Summary

Outpatient parenteral antimicrobial therapy has been used successfully for >2 decades in both children and adults for treatment of a wide variety of infections, including pneumonia, leading to the creation of IDSA practice guidelines for outpatient parenteral antimicrobial therapy [224, 299]. With use of a set of clinical parameters that document no further need for skilled nursing care and with the creation of an outpatient management team—consisting of a pediatrician, skilled pediatric nurse, and pediatric pharmacist—outpatient parenteral therapy for CAP can be successful with a variety of antimicrobial agents [224]. Examples of infants and children who may require ongoing parenteral therapy include those who may have ongoing disease requiring a high serum antibiotic concentration in order to achieve sufficient antibiotic exposure in infected tissues, including those with extensive parenchymal disease, parapneumonic effusions, or lung abscess. Specific criteria to identify children with a need for prolonged parenteral therapy have not been well defined.

No randomized trials have examined the appropriateness of oral compared with parenteral outpatient antibiotic therapy in children with CAP. Selection of oral antimicrobial therapy that is well tolerated and well absorbed, achieving the required antimicrobial exposure at the site of infection, is essential for ongoing outpatient treatment in a compliant family. The risks of adverse events from oral therapy are less than those of intravenous therapy [300].

Early retrospective studies documented the efficacy of oral step-down therapy in children, including children with CAP [225]. More recent studies of oral step-down therapy of osteomyelitis, with some prospectively collected data on treated

Table 10. Areas for Future Research in Pediatric Community-Acquired Pneumonia (CAP)

1. Define the epidemiology of community acquired pneumonia caused by specific bacteria, viruses, atypical bacteria, and disease caused by combinations of ≥1 virus and bacteria for all pediatric age groups, in countries with universal use of protein-conjugate vaccines for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b
2. Define risk factors (epidemiologic, clinical and laboratory) for respiratory failure and hospitalization in the developed world
3. Define mild, moderate, and severe pneumonia for children in the developed world using clinical, laboratory, and oximetry parameters that will enable reliable assessment of the outcome of interventions for each set of children
4. Develop diagnostic tests (on respiratory tract secretions, blood, or respiratory tract tissue) that are noninvasive yet sensitive and specific in documenting clinical disease caused by single pathogens or combinations of pathogens
5. Develop and validate for universal use interpretive criteria for chest radiographs in the diagnosis of pediatric CAP
6. Enhance the ability to track antimicrobial resistance on local, regional, and national levels and communicate these data in ways that can affect local decisions on selecting the most appropriate antimicrobial at the most appropriate dosage
7. Develop diagnostic tests, such as acute-phase reactants, that can validate a clinical impression of severity of disease and can be used to assess appropriate response to therapy
8. Collect and publish data on the expected response of CAP, by pathogen, to appropriately active antimicrobial agents
9. Conduct more studies on the impact of viral testing on patient outcomes and antibiotic prescribing behavior to potentially limit the use of inappropriate antibiotic treatment
10. Assess the role of antimicrobial therapy for atypical bacterial pathogens in pediatrics, particularly for children <5 years of age
11. Develop clinical trial designs that can provide information on the lowest effective antimicrobial dose for the shortest duration of therapy to decrease the development of antimicrobial resistance and the risk of antimicrobial toxicity
12. Develop clinical trial designs that assess the value of combination antimicrobial therapy for severe pneumonia, including combinations that are designed to decrease toxin production in certain pathogens while also inhibiting growth
13. Analyze the cost-effectiveness of each diagnostic and therapeutic intervention for children in the developed world
14. Determine the best imaging techniques for parapneumonic effusions that provide high-quality diagnostic information with minimal radiation exposure
15. Determine which children with parapneumonic effusions require drainage procedures and which procedures are most appropriate for children with complicated effusions
16. Standardize management of thoracostomy catheters with creation of standard criteria for removal of catheters
17. Determine appropriate duration of antimicrobial therapy in children with complicated parapneumonic effusions
18. Determine the criteria required for hospital discharge for children who continue to need antibiotics administered intravenously, intramuscularly, or orally
19. Identify and address barriers to medical care for children with CAP

children, have demonstrated the safety and effectiveness of oral outpatient therapy for serious bacterial infections [301, 302]. Studies have also highlighted the relatively high frequency of complications of peripherally inserted central venous catheters [300], suggesting that parenteral outpatient therapy should be reserved for children who are unable to tolerate (either unable to take or unable to absorb) appropriate oral antibiotics and those with infections caused by resistant bacteria for which appropriate oral antibiotics are unavailable.

PREVENTION

XX. Can Pediatric CAP Be Prevented?

Recommendations

88. Children should be immunized with vaccines for bacterial pathogens including *S. pneumoniae, H. influenzae* type b and pertussis to prevent CAP. *(strong recommendation; high-quality evidence)*

89. All children and adolescents ≥6 months of age should be immunized annually with vaccines for influenza virus to prevent CAP. *(strong recommendation; high-quality evidence)*

90. Parents and caretakers of infants <6 months of age, including pregnant adolescents, should be immunized with vaccines for influenza virus and pertussis to protect the infants from exposure. *(strong recommendation; weak-quality evidence)*

91. Pneumococcal CAP after influenza virus infection is decreased by immunization against influenza virus. *(strong recommendation; weak-quality evidence)*

92. High-risk infants should be provided immune prophylaxis with RSV-specific monoclonal antibody to decrease the risk of severe pneumonia and hospitalization caused by RSV. *(strong recommendation; high-quality evidence)*

Evidence Summary

Infections with *S. pneumoniae* and *H. influenzae* type b are among the most common causes of pediatric CAP worldwide [303, 304]. These 2 pathogens account for approximately half of pneumonia deaths globally in children <5 years old [305]. Infection with both of these pathogens is preventable through immunization. In the United States, pneumococcal conjugate and *H. influenzae* type b conjugate vaccines have been recommended for infants and children as part of the routine infant immunization schedule and have reduced rates of morbidity and mortality from pneumococcal and *H. influenzae* type b pneumonia [306–308]. In 2010, the US Food and Drug Administration approved the 13-valent pneumococcal conjugate vaccine, and the CDC Advisory Committee on Immunization Practices has issued guidelines for the use of this immunization in children [98, 309]. The 13-valent vaccine (PCV13) contains antigen for the 7 serotypes in the PCV7 vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and for 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A). Some of these additional serotypes have been reported in North America,

South America, and Europe and are often implicated in pneumonia, especially pneumonia complicated by empyema or necrosis [89, 236, 250, 258, 310–316]. The licensure of PCV13 may decrease complicated pediatric pneumonia and empyema.

Influenza virus LRTIs in children may be associated with bacterial pneumonia, with or without empyema [260, 317–320]. Immunization with the inactivated trivalent vaccines provides an average vaccine efficacy of ~86% (95% confidence interval, 29%–97%) [321], and live, cold-adapted, attenuated vaccine, provides even greater efficacy in young children 6–59 months of age [322], compared with inactivated trivalent vaccine. The highest rates of protection were documented for years in which the vaccines strains were well matched for circulating strains of influenza in the community, particularly for the inactivated trivalent vaccines.

In children, bacterial pneumonia, particularly pneumococcal pneumonia and, more recently, CA-MRSA pneumonia, has been associated with preceding seasonal influenza virus infection [277, 323, 324]. Complicated pneumonia and empyema have also been associated with historical influenza pandemics [63, 325–327] and the 2009 H1N1 pandemic [259]. The CDC Advisory Committee on Immunization Practices and the AAP currently recommend universal annual influenza immunization for infants and children aged ≥6 months [328]. Universal influenza immunization can decrease pediatric CAP in the United States.

Respiratory syncytial virus is the most common viral etiology of hospitalization for CAP in infants [329]. Studies have documented the ability of palivizumab (Synagis) to decrease the risk of hospitalization due to RSV disease in otherwise healthy, premature young infants and those with medical conditions that place them at greater risk of hospitalization from infection, including chronic lung disease of prematurity, congenital abnormalities of the airway, and neuromuscular disease [330]. Guidelines for the use of palivizumab have been published by the AAP and focus on those most likely to benefit from prophylaxis during the RSV season: the most premature infants and those with comorbid conditions, including underlying lung pathology or congenital abnormalities of the airways, hemodynamically significant congenital heart disease, and neuromuscular diseases [220].

AREAS FOR FUTURE RESEARCH

Throughout these guidelines, it has been noted that high-quality evidence to support recommendations is often lacking. Areas that have been specifically highlighted in the guidelines are summarized in Table 10.

Objective Outcome Measures

Objective outcome measures are needed to guide decisions surrounding initial site of care for patients evaluated in the ambulatory setting and to guide the admission, management, and discharge decisions for hospitalized patients. Outcomes that can be standardized, measured, and compared will allow us to establish benchmarks for the care of children with CAP, with an understanding of the variability in the clinical course between pathogens (bacterial, viral, fungal, tuberculosis, and co-infections), between age groups, between socioeconomic groups, and between those with genetic differences in immune response). In addition, defined outcome measures with current standards of care will enable subsequent documentation of the benefits of new therapeutic interventions.

Relevant outcomes to be considered in the evaluation of children hospitalized with pneumonia include time to resolution of observed clinical and vital sign abnormalities (including fever, work of breathing, respiratory rate, tachycardia, need for parenteral fluid administration, need for surgical intervention, development of pneumonia-associated local, metastatic, or systemic complications, and mortality). Additional outcomes that can be measured to assess the effectiveness of interventions include the requirement for hospitalization, length of hospitalization, readmission after discharge, and costs of care. Few of these outcomes have been considered in studies of childhood CAP. Several, such as the requirement for hospitalization and length of hospitalization, are subjective and may be related to important nonclinical factors, including psychosocial or behavioral considerations, socioeconomic considerations, potential for nonadherence to prescribed therapy, and barriers to follow-up medical care. Others, such as persistence of clinical symptoms, may be related to nonbacterial causes of pneumonia.

Many randomized trials of adults hospitalized with CAP use mortality as the primary outcome measure. Among children, mortality attributable to CAP has decreased by 97% over the past 50 years to <5% of children hospitalized with CAP [331]. In a large cohort of children hospitalized with CAP at 38 tertiary care children's hospitals, only 156 of 20,703 children (0.75%) hospitalized with CAP died [332]. Mortality rates should be examined in all studies of childhood pneumonia, though the infrequency of deaths precludes the use of mortality as a primary outcome measure in the United States and other developed countries.

Directly related to the issue of outcome measures for childhood CAP is the selection of the initial site of care, whether outpatient or in the hospital. This decision is important, because it directly affects the intensity of subsequent testing and therapy. The wide variation in CAP-related admission rates between neighboring geographic regions [333] suggests that physicians do not use consistent criteria to make site-of-care decisions. Unnecessary hospitalization has disadvantages, including nosocomial infection, exposure to ionizing radiation, and increased healthcare costs. However, outpatient management of high-risk patients may increase CAP-associated morbidity rates. As is the

case for CAP in adults [32–35, 38], triage decisions might be facilitated by the creation of clinical prediction rules that identify patients at high or low risk of clinical deterioration and pneumonia-associated complications.

Cost Analysis

The medical costs of caring for a child with CAP are $1464 per episode (in 1997 dollars) [334]. The mean costs for the subset of patients requiring hospitalization are ~$12 000 per episode [335]. Contributing to the family burden are parental days of work loss, ranging from 2 days for CAP treated in the ambulatory setting to 4 days for CAP requiring hospitalization, and family stress, leading to repercussions for parents' health and family morale [336]. Cost is not considered a primary outcome for childhood pneumonia. However, cost may be in important factor in choosing among therapies with similar efficacy. Therefore, studies examining the comparative effectiveness of different treatment strategies for uncomplicated pneumonia and severe pneumonia complicated by parapneumonic effusions, empyema, abscesses or necrosis should examine cost as a secondary outcome measure. Cost analyses may also include nonmedical costs, such as lost parental income.

Long-Term Disability

Few studies have examined long-term outcomes of children with pneumonia. Several longitudinal studies suggest that children with LRTIs in childhood are at higher risk of subsequently developing obstructive lung disease; most of these studies, however, did not confirm the diagnosis of pneumonia with chest radiography, and whether the respiratory tract infection was the cause or consequence of airway hyperreactivity is unclear. Among children with pneumonia complicated by parapneumonic effusion or empyema, scoliosis, though uncommon, may occur but is usually transient. Abnormalities in lung function are common, but no consistent pattern of abnormalities exists, and the sample sizes are too small to enable meaningful comparisons between drainage procedure and lung function abnormalities. Furthermore, because these children were not evaluated for lung function before the diagnosis of pneumonia, it also possible that premorbid conditions involving lung function existed before pneumonia but were assumed by investigators to be the result of pneumonia. Among 36 children with complicated pneumonia evaluated by Kohn et al [337], 19% had mild restrictive lung disease and 16% had mild obstructive lung disease. Among 10 patients studied by McLaughlin et al [338], 26 years ago, 5 patients had a total lung capacity $\geq$1 standard deviation below the mean for age; 1 of these patients was considered to have mild restrictive lung disease (defined as a total lung capacity $\geq$2 standard deviations below the mean for age). In contrast, 7 of the 15 patients studied by Redding et al [339] 20 years ago had evidence of only mild obstructive lung disease, whereas no lung function abnormalities were reported among 13 patients studied by Satish et al [340] just 7 years ago. The impact of the improved quality of care provided by pediatric hospital medicine specialists and pediatric critical care specialists during the past 3 decades is likely to be substantial but remains poorly defined.

Notes

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The recommendations in this report do not represent an official document of the Centers for Disease Control and Prevention. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. IDSA considers adherence to the guidelines listed below to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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