NCC Pediatrics Continuity Clinic Curriculum:
Pneumonia and Bronchiolitis
Faculty Guide

Goals & Objectives:

- To recognize the various etiologies of lower respiratory tract infections (especially by age group)
- To recognize signs and symptoms of pneumonia and bronchiolitis
- To recognize when lab work and imaging might be helpful
- To know criteria for hospital admission and discharge
- To know complications from pneumonia

Pre-Meeting Preparation:

Please read the following enclosure:

- "Management of Pediatric Community-acquired Bacterial Pneumonia" *(PIR, 2017)*
- "Respiratory Syncytial Virus Infection and Bronchiolitis" (*PIR, 2014*)

Conference Agenda:

- *Review* Pneumonia and Bronchiolitis Quiz
- Complete Pneumonia and Bronchiolitis Cases
- **Round-Table Activity:** Pneumonia X-Ray Quiz
  - **Go to PediRad** offered from the University of Bern *make sure you use Google translate (unless you are fluent in German)*
  - Choose "Formation by pathology" from the top tabs, then "Infections" from left column
  - Choose from 80 images. Note "Labeling" and "Full resolution" options.

Post-Conference: *Board Review Q&A*

Extra-Credit:

- www.cchs.net/pediatricradiology (Obtain Login; Complete "Childhood Pneumonia" module under Pediatric Radiology Curriculum, "Chest")
- Management of CAP in Infants & Children . . . *(PIDS & IDSA Guidelines, 2011)*
- Clinical Practice Guideline: The Diagnosis, Management, and Prevention of Bronchiolitis *(AAP, 2014)*
- Uncomplicated Pediatric Community Acquired Pneumonia Pathway *(Children's Hospital of Colorado, 2022)*
- Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic. . . *(MMWR, July 2021)*

Edited by Maj(P) Matt Eberly, Capt Dan Adams, & MAJ Jennifer Hepps. Updated 2022, C. Carr

These two articles are quite long. the resident module includes highlighted versions if you prefer to skim the articles.

Management of Pediatric Community-acquired Bacterial Pneumonia

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Practice Gaps

Management of pediatric community-acquired pneumonia should focus on judicious use of antimicrobial medications, bacterial diagnostics, and surgical drainage when complicated by large effusion and empyema. Treatment in adherence to national guidelines produces favorable outcomes.

Objectives

After completing this article, readers should be able to:

1. Reinforce rational antibiotic use for bacterial community-acquired pneumonia (CAP) in outpatient and inpatient settings.
2. Review and update techniques for microbial diagnosis of CAP.
3. Review medical and surgical management of complicated pneumonia.
4. Present specific considerations for CAP in patients with neuromuscular disease.

INTRODUCTION

Community-acquired pneumonia (CAP) is the most common cause of death in children worldwide, accounting for 15% of deaths in children younger than 5 years of age. (1) Nearly 1 in 500 children will be hospitalized for CAP, which creates a substantial economic burden. CAP is thus important to diagnose and appropriately treat. While viral causes of CAP are most common, differentiating viral versus bacterial etiologies can be difficult. This leads to excessive use of antimicrobial medications or susceptibility to feeling a pressure to prescribe. (2) Overall, in the United States, 11.4 million antimicrobial prescriptions for pediatric respiratory tract infections per year are avoidable. (3) Furthermore, broad-spectrum but less effective antimicrobial agents are often prescribed when pharmacokinetically favorable narrow-spectrum agents are available. (4) Arguably, the untoward effects of overtreatment of CAP in those in whom treatment is unwarranted compounds the morbidity of this disease process. Because of mounting knowledge of antimicrobial side effects, resistance, and microbiome effects, practitioners must adhere to the principles of judicious use when treating CAP. In this regard, CAP, its epidemiology, various etiologic origins, clinical

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ABBREVIATIONS

CAP	community-acquired pneumonia
CT	computed tomography
IV	intravenous
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
PCR	polymerase chain reaction
VATS	video-assisted thorascopic surgery

presentations, and general diagnosis and treatment were thoroughly reviewed in this journal (5) and are also discussed at length in national guidelines. (6) The intent of this review is to supplement this excellent work by focusing on specific treatment once a provider has weighed the risks and benefits and decided that a child's condition warrants treatment of bacterial CAP and management of its complications. Salient details from both sources are summarized throughout.

REVIEW OF INITIAL DIAGNOSIS

No standard of reference for diagnosis or single definition of pneumonia exists. In this review, CAP is defined as an acute lower respiratory tract infection acquired in a previously healthy individual. Associated symptoms include fever, cough, dyspnea, and tachypnea with supporting evidence of parenchymal infection and inflammation, diagnosed according to findings at chest auscultation or the presence of focal opacity seen on chest radiographs. (5)(7) Focal opacity on chest radiographs is often held as a standard of reference; however, some viral processes and atelectasis can cause focal radiographic findings (though atelectasis traditionally resolves in 48–72 hours). In addition, findings on radiographs can lag behind clinical symptoms. Viral pneumonitis accounts for most respiratory infections, particularly in children younger than 5 years of age. Unfortunately, no constellation of clinical symptoms or signs (fever, tachypnea, hypoxemia, work of breathing) displays good specificity or sensitivity for radiographic findings of pneumonia, except that symptom severity and ill appearance do correlate with focal infiltrates. To exclude pneumonia, investigators in 1 study assessed the absence of cough, crackles (rales), rhonchi, retractions, and nasal flaring in young infants and found it useful in its negative predictive value; but again, the presence of these findings was insensitive in the prediction of pneumonia at radiography. (8) Left with few alternatives, pediatricians typically use a combination of radiographic and physical findings to decide to treat a patient for bacterial disease. Decisions on whether to hospitalize a patient are made by weighing the criteria presented in Table 1, which were adapted from national guidelines and prior review articles. (5)(6)

When to perform imaging in cases of acute pneumonia is not well delineated, although some rules of thumb apply. Chest radiographs are indicated in patients with more severe respiratory distress, particularly those who meet criteria for hospitalization. This imaging modality is used to assess the presence of focal parenchymal opacities, as well as screening for the presence of complications such as effusion or empyema in patients who have not responded to antibiotic treatment. Per Infectious Disease Society of America guidelines, other indications for chest radiography include inconclusive clinical findings and ruling out other possible causes of respiratory distress that can be diagnosed at radiography (foreign body, pneumothorax, pleural disease, or cardiac disease, including pulmonary edema and cardiomegaly). Imaging is also indicated in febrile infants without a source who are younger than 12 months of age, if there is evidence of leukocytosis. Conversely, in patients with mild evidence of lower respiratory tract infection (fever, cough) without hypoxemia or a focal lung examination who are stable for outpatient treatment, radiographs of the chest are not typically indicated. (9)(10)

Laboratory examinations are considered for all patients ill enough to be hospitalized with suspected bacterial pneumonia. These may commonly include blood cultures, inflammatory markers, complete blood cell count, and nasopharyngeal swab polymerase chain reaction (PCR) for viruses. Blood cultures rarely yield positive findings in CAP, and they should not be performed in patients treated on an outpatient basis or in hospitalized patients with uncomplicated disease. However, in patients with severe disease, the 10% to 18% yield is arguably worthwhile. (11) Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein level, or procalcitonin) may aid in clinical decision-making if measured longitudinally, particularly in those with complicated CAP (discussed later). (12) The complete blood cell count may provide information on further complications, such as thrombocytopenia or anemia from hemolytic uremic syndrome. (6) Nasopharyngeal swabs for viral PCR should only be performed if the results will change management. The number and types of examinations performed depends on the severity and trajectory of the illness. A thorough history may lead one to consider testing for other unusual causes of lobar pneumonia. These causes and their historical cues are listed in Table 2.

In the remainder of this review, it is assumed that a practitioner has weighed the clinical, radiologic, and laboratory evidence for their patient as discussed earlier, reviewed national guidelines, and made a judicious decision to treat bacterial causes of CAP. With this context in mind, we will discuss pathogenesis, outpatient and inpatient management with respect to routine and novel diagnostics, antimicrobial choices and length of therapy, diagnosis and management of complications, and recurrent lobar pneumonia and special CAP considerations for patients with neuromuscular disease.

PATHOGENESIS AND BASIC DEFINITIONS

Pneumonia occurs as result of invasion of the lower respiratory tract by a pathogenic organism. Bacterial infection

TABLE 1. **Criteria to Consider Hospitalization for Pediatric Pneumonia**

• Hypoxemia (oxygen saturations <90% to 92% at sea level)
• Infants <3 to 6 months of age with suspected bacterial community-acquired pneumonia
• Tachypnea:
◦ Infants <12 months of age: respiratory rate >70 breaths per min
◦ Children: respiratory rate >50 breaths per min
• Respiratory distress: apnea, grunting, difficulty breathing, and poor feeding
• Signs of dehydration or inability to maintain hydration or oral intake
• Capillary refill time >2 s
• Infants and children with toxic appearance
◦ Suspected or confirmed to have infection with a virulent organism (community-acquired methicillin-resistant *Staphylococcus aureus* or group A *Streptococcus*)
• Underlying conditions/comorbidities that:
◦ May predispose patients to a more serious course (eg, cardiopulmonary disease, genetic syndromes, neurocognitive disorders, neuromuscular disorders)
◦ May be worsened by pneumonia (eg, metabolic disorder)
◦ May adversely affect response to treatment (eg, immunocompromised host, sickle cell disease)
• Complications (eg, effusion and/or empyema)
• Failure of outpatient therapy (48–72 h with no clinical response)
• Caretaker unable to provide appropriate observation or to comply with prescribed home therapy
Indications for intensive care unit admission include:
• Severe respiratory distress or impending respiratory failure that requires:
◦ Intubation and mechanical ventilation
◦ Positive pressure ventilation
• Recurrent apnea or slow irregular respirations
• Cardiopulmonary monitoring due to cardiovascular compromise secondary to:
◦ Sustained tachycardia
◦ Inadequate blood pressure
◦ Requirement of pharmacological support for blood pressure or perfusion
◦ Altered mental status due to hypercarbia or hypoxemia
◦ Pulse oximetry measurement of <92% on fractional inspired oxygen concentration of >0.50
• Pediatric Early Warning Score >6

Reproduced with permission from Gereige RS, Laufer PM. Pneumonia. Pediatr Rev. 2013;(34):19. (5)

represents a failure of many layers of extrinsic and intrinsic defense. Physical barriers to infection include upper respiratory tract nasal hairs and turbinate architecture, as well as complex respiratory airway branching that inhibits access to distal airways. In the large airways, cough and mucociliary clearance of secretions and humoral and cell-mediated defenses work to defend the lower respiratory tract from invasion. Secreted and humoral immunoglobulins, as well as intrinsic antimicrobial properties of alveolar fluid, work with the phagocytic alveolar macrophages to eradicate bacteria. When these defenses are overwhelmed in some capacity, bacterial pathogens penetrate and cause disease. (13)

Many factors may contribute to overwhelming of these defenses and subsequent pneumonia, but the influence of

TABLE 2. **Unusual Causes of Pneumonia in Children: A Summary of Historical Clues**

AGENT	HISTORICAL CLUES	SUMMARY OF INCUBATION, DIAGNOSTICS, AND TREATMENT (CONSULT REFERENCES FOR DETAILS)[a]
Bacillus anthracis	Exposure to contaminated hides (including drum covers); often will have skin manifestation (eschar), as well	Incubation: 2–43 d Diagnostic: culture[b] and PCR Treatment: ciprofloxacin, doxycycline
Blastomyces dermatitidis	Travel to Central United States	Incubation: 2 wk to 3 mo Diagnostic: culture[b], serologic analysis Treatment: amphotericin
Chlamydophila psittaci	Exposure to sick birds	Incubation: 5–14 d Diagnostic: serologic analysis Treatment: doxycycline, azithromycin second line
Coccidioides immitis	Travel to endemic area (Arizona, Nevada, California, Texas, Utah, Mexico, Central and South America)	Incubation: 1–4 wk for primary infection, disseminated disease weeks to years Diagnostic: culture[b], serologic analysis Treatment: not always needed, but fluconazole, itraconazole, amphotericin B
Coxiella burnetti	Exposure to infected birthing fluids or excreta (including unpasteurized milk) from sheep, cattle, and goats	Incubation: 14–22 d Diagnostic: PCR and serologic analysis, best if acute and convalescent Treatment: doxycycline best, second-line TMP-sulfa
Cryptococcus gatii	Travel to endemic area (Pacific Northwest)	Incubation: 8 wk to 13 mo Diagnostic: culture[b] Treatment: amphotericin
Entamoeba histolytica	Exposure to contaminated food, most commonly in resource-limited settings, institutionalized settings, or men who have sex with men; occurs in conjunction with liver abscess or triad of liver abscess, parapneumonic effusion, pericardial effusion	Incubation: days to years, most commonly 2–4 wk Diagnostic: identification of organisms in sample, serology Treatment: metronidazole plus luminal amebicide
Francisella tularensis	Exposure to ticks and potentially horseflies or sick animals (most notoriously rabbits); history of lawn-mowing over carcasses	Incubation: 1–21 d (typically 3–5 d) Diagnostic: culture[b], PCR of blood or source, serologic analysis Treatment: aminoglycoside, ciprofloxacin
Hantavirus	Exposure to mice feces and/or urine in endemic area (Colorado, Utah, New Mexico, Arizona); often hemoconcentration with thrombocytopenia	Incubation: 1–6 wk Diagnostic: serologic analysis Treatment: supportive
Histoplasmosis	Travel to endemic area (Central United States), exposure to birds and/or bird excrement	Incubation: 1–3 wk for primary infection, disseminated disease weeks to years Diagnostic: culture[b], serologic analysis, urine antigen Treatment: not always needed, but if so amphotericin B, itraconazole
Legionella pneumophila	Exposure to contaminated water supply	Incubation: 2–10 d Diagnostic: culture, antigen in urine, serologic analysis Treatment: azithromycin, levofloxacin
Leptospira spp	Exposure to urine (or water contaminated with urine) of infected animals; usually some liver involvement, as well	Incubation: 2–30 d, usually 5–14 d Diagnostic: serologic analysis Treatment: penicillin
Mycobacterium tuberculosis	Exposure to infected persons or high-risk settings or to persons with chronic cough with such exposures	Incubation: highest risk for disease first 2 y after infection, but can be years Diagnostic: culture, rapid diagnostics, clinical Treatment: 4 drugs, see references
Mycoplasma pneumoniae	Exposure to infected person 1–4 weeks ago	Incubation: 1–4 wk (usually 2–3 wk) Diagnostic: PCR (preferred), serum immunoglobulin M Treatment: azithromycin

Continued

TABLE 2. (Continued)

AGENT	HISTORICAL CLUES	SUMMARY OF INCUBATION, DIAGNOSTICS, AND TREATMENT (CONSULT REFERENCES FOR DETAILS)[a]
Yersinia pestis	Exposure to infected animals, including prairie dogs, squirrels, ill cats and dogs, fleas 85% of US cases are in New Mexico, Colorado, Arizona, and California —	Incubation: 1–8 days Diagnostic: culture[b], PCR, serologic analysis Treatment: doxycycline, ciprofloxacin second-line TMP-sulfa

TMP-sulfa=trimethoprim/sulfamethoxazole.

[a] *Information for consideration of differential only; practitioners should refer to the AAP* Red Book *and national guidelines. Timing of positive serologic findings varies, and some diseases require acute and convalescent sera. Some organisms require specific culture conditions. Treatment regimens may depend on location and severity of disease.*

[2] *Alert the laboratory if a specimen will be sent for culture that has a high risk of infection for laboratory personnel.*

viral coinfection on bacterial pneumonia is an important concept. Animal models suggest that respiratory viruses destroy the respiratory epithelium and change the landscape of the cell surface to exhibit more antigen receptors. These changes impair the cough reflex and mucociliary clearance. In addition, viruses may inhibit normal macrophage function. Influenza is most commonly associated with subsequent bacterial superinfection, but suspicion for this entity should be high in any child with a viral prodrome who exhibits abrupt worsening of clinical status in a time frame in which a viral infection should be resolving. (14) A public health example of this viral-bacterial interplay is readily available, in that pneumococcal vaccines decrease the morbidity of influenza infections, while some viral vaccines decrease the incidence of radiographic findings of pneumonia. (15)

Bacterial pneumonia can be classified according to several pathophysiological definitions based primarily on radiologic and physical findings. Lobar pneumonia involves a single discrete lobe or lung segment of parenchymal inflammation, a discrete opacity on chest radiographs, and focal findings of crackles, bronchial breath sounds, and diminished aeration at auscultation. This classic pattern is typical of pneumococcal infection. Bronchopneumonia involves inflammation of the airways and interstitium and appears more diffuse on images, with scattered crackles, rhonchi, and asymmetrical aeration at examination, commonly associated with *Streptococcus pyogenes* or *Staphylococcus aureus*. Mixed peribronchial and interstitial disease with focal parenchymal inflammation is observed in cases of viral pneumonia that become subsequently bacterial (in patients with influenza, for example). Cavitary pneumonia is a result of tissue necrosis associated with *Mycobacterium tuberculosis*, although it can occur with other pathogens. (13) Complicated pneumonia includes parapneumonic effusions, pulmonary abscesses, bronchopleural fistulas, and necrotizing pneumonia.

CAUSATIVE PATHOGENS AND THEIR IDENTIFICATION

Definitive identification of bacterial etiologic origins in CAP is limited by lack of a primary sample for culture or PCR from the lower respiratory tract. This in turn limits our ability to describe with confidence the microbial and epidemiological patterns of bacterial pneumonia. That said, bacterial causes of CAP continue to include *Streptococcus pneumoniae*, *S aureus*, and *S pyogenes*. Overall, with the advent of *S pneumoniae* vaccines, the incidence of unequivocal bacterial CAP is decreasing, although of those who develop CAP, *S pneumoniae* remains the most common cause. Multiple studies in which antigen detection and nucleic acid PCR were used on culture-negative empyemas demonstrated that most culture-negative empyemas are caused by penicillin-susceptible, nonvaccine serotypes of *S pneumoniae*. (13)(16)(17) For *S aureus*, there is some evidence that pediatric lung infections from methicillin-resistant *S aureus* (MRSA) are increasing. (18)(19)(20) Because of immunization, herd immunity, and partial immune responses to even 1 dose of vaccine, invasive disease due to *Haemophilus influenzae* type B is now exceedingly uncommon. Nontypeable *H influenzae* strains are now responsible for most cases of invasive *Haemophilus* disease, including pneumonia. (21) Between 2003 and 2012, the annual incidence of invasive, nontypeable *H influenzae* disease was 1.6 cases per 100,000 children younger than 5 years of age. Invasive disease with *Moraxella catarrhalis* is similar. Studies on the evaluation of the role of these organisms are marred by easy contamination from the upper airway, and results are difficult to interpret. It is likely

that these organisms play a small role in unequivocal bacterial CAP, and that when they do, disease is likely to be less severe. *Mycoplasma* undoubtedly causes CAP and can cause lobar disease and effusions, although the role of treatment remains controversial (as discussed later). A list of less usual causes for pneumonia and when to consider them is presented in Table 2.

Inexpensive, reliable, noninvasive methods for establishing a bacterial etiologic origin in pediatric pneumonia are highly desirable to promote selection of the most narrow and effective antimicrobial treatment. Options for pathogen discovery include upper and lower airway samples, coupled with traditional culture methods, targeted PCR, and targeted relative quantitative PCR (although these PCR methods are not yet available except in research settings).

Upper-airway samples include nasopharyngeal washes and swabs and throat samples. These samples are useful in the detection of various bacteria, including *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis,* and *Bordatella parapertussis*. Sputum expectoration is commonly used in adults but has been a challenge in pediatrics. In theory, sputum includes a lower airway sample. Sputum samples are informative in adults and have been studied with success in children as young as 1 month of age. (22) Coordination with a respiratory therapist to use specialized techniques to improve sputum expectoration and/or nasal aspiration may be required in children younger than 6 years of age to obtain a successful, high-quality specimen (fewer than 10 squamous epithelial cells per low-power field). While sputum collection is not necessary for evaluation in a patient treated on an outpatient basis, attempts should be made to obtain sputum in children with moderate to severe pneumonia who are hospitalized. (6) Low-quality sputum specimens are not meaningful, can be misleading, and should not be cultured. (13)(23) Studies of PCR of sputum and upper-airway samples are plagued by the bias of pretreatment and lack of comparison to the lower airway. In theory, these are improved by using quantitative PCR but are still problematic and are not yet readily available. (24)

Sampling techniques for the lower respiratory tract include direct pleural sampling, pleural fluid aspiration after placement of a chest tube or video-assisted thorascopic surgery (VATS), bronchoalveolar lavage via flexible bronchoscopy, or (rarely performed) direct biopsy of the parenchyma or open thoracotomy.

Sampling of pleural fluid without placement of a chest tube (thoracentesis) is the most direct way of obtaining more information but has become unfamiliar for many practitioners. For a period of time, it was believed that identifying the microorganism did not change the treatment, and amid concerns about surgical complications such as pneumothorax, bleeding, and pain, the practice has become much less common. In the current era of antimicrobial resistance, this should be reconsidered. Ideally, sampling should occur before treatment with antibiotics. Procedural instructions for thoracentesis and recommendations for radiologic assistance are available. (25) Commonly, pleural fluid is obtained with therapeutic procedures such as chest tube placement or VATS, which almost always occur after some period of antimicrobial therapy, often resulting in negative culture findings.

When pleural fluid is obtained, it should be sent for Gram stain and bacterial culture, as well as cell count and differential, to allow differentiation of bacteria from other causes of effusion (ie, mycobacterial, oncologic). Modified criteria, originally proposed by Light et al, (26) in 1972, allow differentiation of exudate from transudate on the basis of fluid pH level, presence of leukocytes, protein, glucose, and lactate dehydrogenase ratios. However, international guidelines do not recommend these tests because they rarely change management in pediatric cases with a high pretest probability of bacterial pneumonia. Culture of the fluid is crucial; however, if the patient is pretreated, 70% of findings are negative. (10) *S pneumoniae* is a particularly difficult bacterium to culture because of its propensity for autolysis and relative fragility during sample transport. (27) Other cultures should be based on unusual exposure history or clinical situations (Table 2).

Efforts to better characterize the bacterial components of pleural fluid with culture-independent methods are underway. Many studies focus on identification of *S pneumoniae* in culture-negative pleural samples via PCR-based identification. Antigen testing and PCR testing of pleural fluid greatly increase diagnostic yield, although these are not yet readily available. (15) A study in which uniplex PCR was used in pleural fluid demonstrated a causative organism in 82% of 56 children. (28) In addition to targeted PCR, relative quantitation of PCR, PCR for the gene-encoding bacterial 16S ribosomal RNA subunit, and deep sequencing are all up-and-coming techniques. (29) Urinary antigen tests for *S pneumoniae* are not recommended for children because of the high rate of false-positive results. (6)

In patients receiving mechanical ventilation, 2 additional options exist for obtaining lower respiratory tract specimens: bronchoscopy and tracheal aspirate. Tracheal aspirates are likely of similar utility to sputum and are most useful if obtained early, prior to colonization of the endotracheal tube with patient or hospital flora. The use of bronchoscopy to obtain a bronchoalveolar lavage sample is an option if other sources of microbial diagnosis cannot be obtained and should be particularly considered in complicated and/or immunosuppressed

hosts who may have unusual pathogens or in children who are not improving despite receiving adequate therapy for usual pathogens. In pediatrics, nonbronchoscopic bronchoalveolar lavage or mini–bronchoalveolar lavage has been studied for safety in older children (30) with ventilator-associated pneumonia but is not commonly used because of the size of the pediatric airway. (31)

OUTPATIENT MANAGEMENT

Uncomplicated bacterial pneumonia is an entity that can be effectively treated in most children on an outpatient basis with oral antibiotics and supportive care. Cough and fever are often present in any patient in whom pneumonia is being considered, but the degree of respiratory distress is important to assess for each patient. (32)

For management of outpatient mild to moderate bacterial pneumonia, treatment with antibiotics is empirical; it is not recommended to pursue tests to assess for a cause if the patient does not meet criteria for inpatient treatment. Criteria for hospitalization include hypoxemia, moderate respiratory distress, age younger than 12 months, and presence of a moderate to large pleural effusion, in addition to the criteria in Table 1. (5)(6) A child who meets the criteria for outpatient management will thus be relatively well and amenable to oral therapy but at risk for progression; thus, close follow-up is warranted.

A key to success in the outpatient realm is an appropriate choice and dose of an antimicrobial agent. Selection of appropriate oral antibiotics is based on assessment of presumed pathogens, patient age, exposures, prior medical history, medication allergies, and community bacterial resistance patterns. The key organism to cover in this setting is *S pneumoniae* because it remains the most common cause, despite vaccination. (15) The cornerstone of oral antimicrobial treatment for *S pneumoniae* is amoxicillin. Practitioners commonly presume that oral cephalosporins are superior to amoxicillin for *S pneumoniae*; this likely stems from knowledge that some *S pneumoniae* penicillin nonsusceptible isolates are susceptible to ceftriaxone and assume that oral cephalosporins are superior to amoxicillin. Indeed, the opposite is true. Oral cephalosporins have short half-lives, are poorly absorbed, are highly protein bound, and are often dosed at long intervals. This results in serum concentrations that do not provide enough killing time (serum concentration over minimum inhibitory concentration [MIC]) to treat, except for organisms with a low MIC to a selected drug. Amoxicillin reaches higher levels and is less protein bound, thus giving it more time with a drug concentration over the MIC for many pathogens, provided the MIC is in the susceptible or intermediate drug level range. Because the pharmacokinetics of the oral cephalosporins are far inferior to amoxicillin, their use in CAP should be reserved for patients who are allergic to penicillin or patients with a cause known to be resistant to amoxicillin but susceptible to cephalosporins (ie, *M catarrhalis* or β-lactamase–positive *H influenzae)*. (6)(33)

Another consideration for treatment with β-lactam antibiotics is the dosing interval. Many practitioners are unaware that more frequent dosing will provide more killing time and have the potential to treat organisms with slightly higher MICs. For example, for *S pneumoniae* with a penicillin MIC of 2.0 μg/mL, 90 mg per kilogram of body weight divided into doses administered twice daily will achieve cure in approximately 65% of patients, while if divided into doses administered 3 times daily, it is estimated to provide cure in 90%. (34) Thus, when amoxicillin is used, pharmacokinetics are superior if used in high doses (90–100 mg/kg per day) divided into doses administered 3 times a day, instead of twice daily. This dosing strategy should be selected where higher rates of nonsusceptible *S pneumoniae* exist or arguably in all patients with lobar CAP in whom room for error with outpatient treatment should be minimized. (35) Although twice-daily dosing is successful in otitis media because of the prolonged half-life of the drug in the ear fluid (and thus creating more time with a drug level over the MIC of the offending organism) when compared to serum (4 vs 1.2 hours, respectively), this cannot be safely extrapolated to true bacterial pneumonia. (36)

Although empirical coverage of *H influenzae* and *M catarrhalis* is not warranted in most patients, it is important to note that 30% of *H influenzae* and 100% of *M catarrhalis* produce a β-lactamase, rendering those isolates resistant to amoxicillin. They are routinely susceptible to amoxicillin–clavulanic acid and cephalosporins. Other microbial causes of CAP include *S aureus* and *S pyogenes,* although these bacteria do not usually cause disease mild enough to be treated in an outpatient setting. Oral antimicrobial selections are discussed in Fig 1.

M pneumoniae is known to cause diffuse or lobar CAP, but the benefits of treatment remain controversial. (37)(38) The ability of a practitioner to differentiate *Mycoplasma* from other etiologic origins by using clinical history and examination findings is not reliable and can lead to overtreatment of this pathogen. Although national guidelines recommend consideration of treatment in patients older than 5 years of age, (6) this may lead to undue pressure to treat, given the lack of proven benefit. The judicious practitioner should be allowed room to align with national reviews (38) and not routinely treat this entity empirically, particularly if symptoms

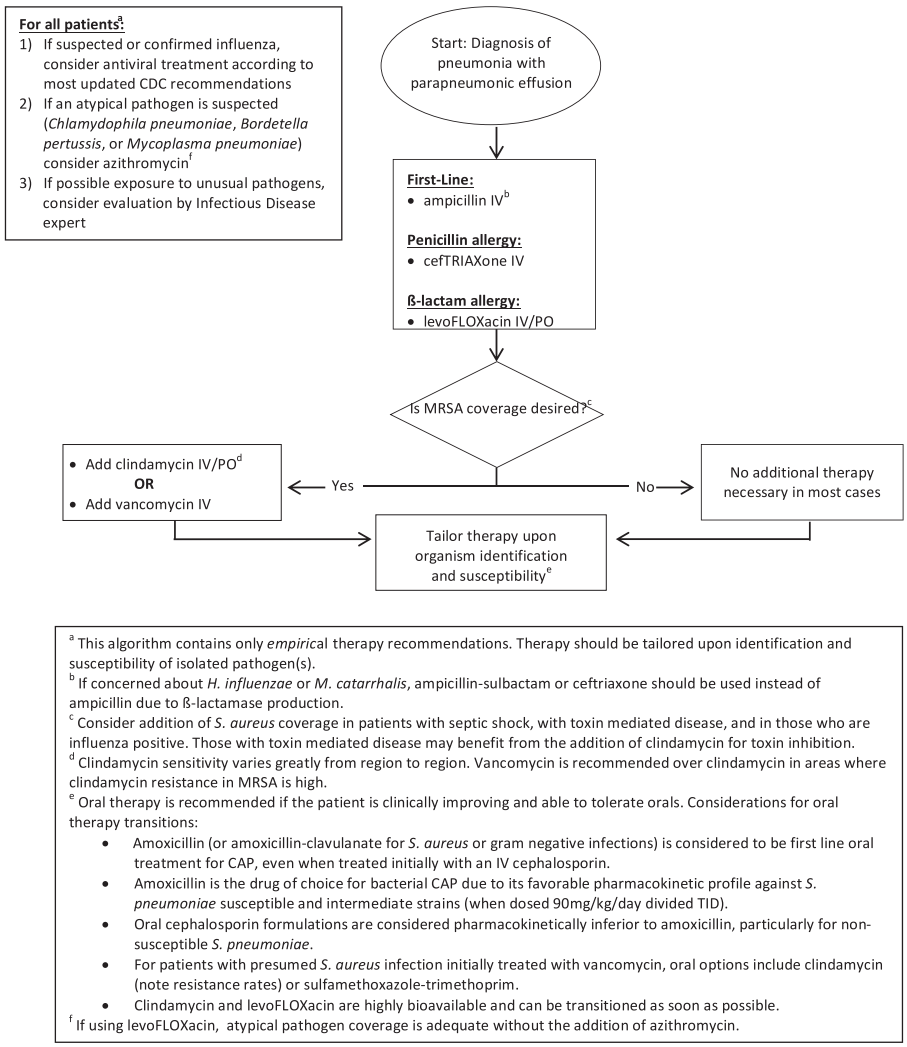

Figure 1. Complicated CAP empirical antibiotic therapy algorithm. Adapted from Complicated Community Acquired Pneumonia, Clinical Care Guidelines, Children's Hospital Colorado, updated October 11, 2016. (71) CAP=community-acquired pneumonia, CDC=Centers for Disease Control and Prevention, IV=intravenous, MRSA=methicillin-resistant *Staphylococcus aureus,* PO=per os, TID=3 times daily.

are also consistent with viral disease or if providers are already treating the patient for other bacterial causes. In adult populations, the desire to cover both *Mycoplasma* and bacterial causes has led to a crisis in the overuse of fluoroquinolones, a practice the Food and Drug Administration has strongly discouraged. (39) Though azithromycin is largely ineffective against the traditional CAP pathogens mentioned earlier, it is often used in an attempt to treat both typical and atypical infections, which contributes to the fact that it is the second most commonly prescribed antimicrobial agent in outpatient pediatrics. (40) Despite a recent publication in which investigators suggest that azithromycin may decrease subsequent wheezing when used in early childhood, (41) the difficulties of this research make the results inconclusive, and any potential benefit must be weighed against the need for dual therapy, side effects, development of resistance, and detrimental effects on the microbiome. (42)(43) Many centers now have rapid diagnostics to target *M pneumoniae*, so treatment might logically be reserved for hospitalized patients with positive PCR test findings.

Length of therapy for uncomplicated bacterial CAP should not exceed 7 days, and there are data to support 3 days for nonsevere CAP. (44) Studies have demonstrated similar success rates of 7 days when compared with 10 days and 5 days. (45)(46) Although all studies involving CAP are subject to the Pollyanna phenomenon (positivity bias), (47) the number and consistency of the shorter therapy studies increase the quality of the evidence such that the benefits (in terms of mitigating resistance, decreased side effects, and compliance) of 5 or 7 days should make these lengths standard.

A patient is considered to have failed outpatient antimicrobial therapy for CAP when clinical worsening occurs,

despite 48 hours of properly chosen and dosed antimicrobial agents. Notably, fever may persist (for an average of 48 hours), (48) but if a patient is improving in other ways (better oral intake, lower respiratory rate, increased normal activities), this would not be deemed a failure. If failure occurs, repeat chest radiography and consideration of hospitalization are in order. If the patient is hospitalized, it is not necessary to expand coverage unless resistant organisms are suspected (ie, rapid progression suggestive of *S aureus* or *S pyogenes*), since intravenous (IV) ampicillin reaches much higher serum levels than amoxicillin and provides extended killing time for *S pneumoniae*. One may suspect highly resistant *S pneumoniae* in children who have not received the pneumococcal conjugate vaccine PCV13, since they are not immunized against serotype 19A.

INPATIENT MANAGEMENT

Inpatient management of CAP can be separated into 2 patient scenarios: those who are admitted with viral pneumonitis and who might have superimposed CAP and those with a clear need-to-treat bacterial CAP, with or without a parapneumonic process. For the first category, the discussion of diagnosis, outpatient management, and hospitalization criteria in Table 1 was addressed earlier. For those with an undisputed need-to-treat bacterial CAP as the primary diagnosis, a few management principles apply. These include diligence in solidifying a microbial diagnosis, thoughtful antimicrobial therapy, and management of complicated disease.

Although inpatient bacterial CAP is still most likely to be *S pneumoniae*, other causes should be considered in certain inpatient settings. *S aureus* should be particularly considered in patients with influenza and superimposed CAP. *S aureus* and *S pyogenes* should be considered in those with rapidly progressive disease or signs and/or symptoms of sepsis or toxic shock. While ampicillin provides adequate coverage of *S pyogenes*, coverage for inpatients may need to be expanded for *S aureus* with consideration of MRSA coverage, depending on severity of disease and local resistance patterns. The need to cover *H influenzae* or *M catarrhalis* specifically in the inpatient setting in normal hosts is debatable, and hospitals that choose to prioritize the use of ampicillin and/or amoxicillin (which lack coverage for 30% of *H influenzae* and all *M catarrhalis*) demonstrate similar outcomes when compared to the historical use of more expanded regimens. (49) *S pneumoniae, S aureus,* and *S pyogenes* can all cause parapneumonic processes. For antibiotic treatment guidelines for inpatient CAP, please see Fig 1 on antibiotic choice (IV and oral step-down).

Studies support the use of standardized inpatient CAP guidelines. Per the Centers for Disease Control and Prevention Study of Etiology of Pneumonia in the Community on pneumonia causes, the use of inpatient clinical care guidelines improved the use of ampicillin and decreased use of cephalosporins and macrolides without negatively affecting outcomes. (50) In this study, investigators also looked at combined clinical physiological parameters (respiratory rate, oxygen saturation) for "time to clinical stability" and reported that guidelines were also helpful in determining timing of discharge. (51)

Given that moderate to severe CAP involves bacteria-triggered inflammation, investigations into adjunctive anti-inflammatory therapies have included macrolides and corticosteroids. Adjunctive corticosteroid use is supported in adults with severe CAP, with studies showing shorter time to clinical stability, shorter hospital lengths of stay, and possible decreased mortality. There were no clinically significant side effects identified in relation to corticosteroids in these patients. (52)(53) The use of corticosteroids has not yet been studied in pediatric CAP and should thus be approached with caution. A short steroid course (5–7 days) should be strongly considered in patients with CAP who received a diagnosis of asthma if they exhibit signs of reversible airway obstruction. Use of azithromycin as an anti-inflammatory agent in acute CAP remains controversial and is not recommended at this time. (54)(55)

COMPLICATED PNEUMONIA

There is substantial variability in admission rates for children seen in the emergency department for CAP independent of illness severity, and there is little to help clinicians predict which patients will go on to develop moderate to severe complications. In a recent study in *Pediatrics*, in which the Centers for Disease Control and Prevention Study of Etiology of Pneumonia in the Community data were also used, predictive analytics were used to develop 3 prognostic models to estimate risk for severe pneumonia outcomes in children. A simple electronic health record model in which 9 predictors were aggregated, including data on age, race, temperature, vital signs, and partial pressure of arterial oxygen to fractional index of oxygen ratio, was used to accurately identify risk for intensive care unit admission and severe outcomes, including the need for invasive mechanical ventilation and death. This work, despite requiring more validation, may provide an important tool for clinicians in determining those at highest risk for complications from CAP. (56)

Despite decreasing incidence of bacterial pneumonia and invasive pneumococcal disease attributed to vaccination

against *H influenzae* and *S pneumoniae*, studies indicate that the rate of empyema and other complications of bacterial CAP are increasing, particularly in preschool-aged patients. (18)(57) This is possibly due to pneumococcal serotype replacement and/or antibiotic resistance. (58) Complications of CAP include parapneumonic effusion, empyema, pulmonary abscess, bronchopleural fistula, necrotizing pneumonia, acute or impending respiratory failure, and sepsis. Please refer to Fig 2 for radiographic examples of some of these complications. *Parapneumonic effusion* refers to an exudative process that results in a pleural fluid collection due to pneumonia. Parapneumonic effusions develop in stages on the basis of duration. In the first several days, effusions are exudative and free flowing. By the second week, they become fibropurulent with fibrin deposition over the pleurae. Fluid can become septated. By 10 to 14 days, the effusion becomes organized, with a stiff pleural membrane. Empyema is a purulent effusion, with leukocytosis and/or bacteria in the pleural space. Effusions are categorized by size to aid in clinical decision-making (Fig 3). A bronchopleural fistula occurs when an erosion in the airway or parenchyma communicates directly with the pleura, such that air enters the pleural space. Necrotizing pneumonia occurs as a complication of both lobar and bronchopneumonia and is defined by a combination of parapneumonic effusion, loculation, and septation of the effusion and abscesses. These patients have a combination of the findings discussed earlier, exhibit diminished or absent aeration and crackles at auscultation, and typically appear ill and even toxic, with high fevers, hypoxemia, and malaise. Complicated CAP should be suspected in cases of previously healthy children with prolonged and persistent fever or deteriorating clinical status, despite receiving appropriate antibiotic treatment. Other clinical scenarios—such as rapid progression to impending or fulminant respiratory failure—or the presence of chronic comorbid illness—such as immunodeficiency, chronic lung disease, or anatomic abnormalities—should prompt earlier consideration and evaluation with imaging and laboratory diagnostics.

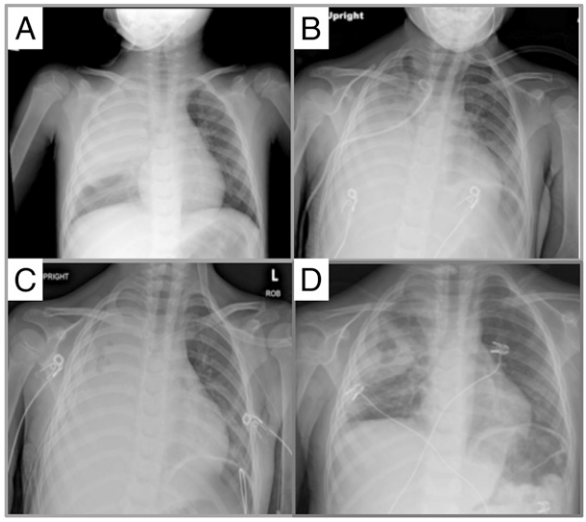

Figure 2. Radiologic progression of complicated pneumonia. A. Radiograph obtained on August 24 shows right upper lobe opacity and small right pleural effusion. B. Radiograph obtained on August 29 shows right middle and lower lobe consolidation and right-sided pleural effusion with chest tube. C. Radiograph obtained on August 30 shows worsening consolidation of the right upper lobe with minimal central lucencies, likely an underlying component of pleural effusion. A chest tube is in place. D. Radiograph obtained on September 3 shows improved aeration with lucencies within the consolidation of the right upper lobe, which suggests cavitation with small right effusion.

Indications for chest computed tomography (CT) in complicated CAP include concern for abscess or other parenchymal abnormality. Identification of pleural septations as evidence of organized pleural effusion or empyema is not reliable and does not correlate with outcomes of specific interventions (ie, chest tube drainage, intrapleural fibrinolytics, or VATS). Therefore, chest CT is not indicated on a routine basis for evaluation of mild to moderate pneumonia or even in cases of simple pleural effusion. When indicated, CT should be performed with IV contrast material to allow differentiation of thoracic structures.

The utility of lung ultrasonography in diagnosing complicated pneumonia is controversial, in both the literature and clinical practice. Lung ultrasonography in combination with initial chest radiography can demonstrate small pneumonic consolidations and allow early diagnosis of pleural effusion. (59) Evaluation of pleural effusion with chest ultrasonography may *(a)* allow localization, *(b)* demonstrate the presence of loculations or septations to further characterize empyema, and/or *(c)* guide thoracentesis and drain placement. However, the presence or absence of septations on ultrasonography does not enable prediction of a response to specific therapies or indicate a need for surgical intervention over medical management. Ultrasonography is highly user dependent, and images should be acquired and interpreted by experienced personnel.

Management of parapneumonic effusions may be solely medical or may involve a range of procedures to drain fluid and physically disrupt fibrosis and inflammation. The decision of type and timing for percutaneous drainage or surgical intervention often depends on local expertise and the individual clinical scenario. Long-term outcomes of children with pleural empyema are good, regardless of the treatment approach used during the acute phase of illness, (58) although drainage procedures that meet the criteria as outlined in national recommendations may shorten hospital stays. (13) An example of an algorithm based on these guidelines is provided in Fig 3 and is used at our institution. The goal of

drainage is to debulk disease to provide symptomatic relief and to allow antimicrobial agents to penetrate poorly perfused areas.

Criteria for surgical intervention in cases of parapneumonic effusion and empyema involve consideration of the size and duration of the effusion on images and the degree of respiratory compromise and illness severity. Patients with clinically significant hypoxemia, hypercapnia, and positive pressure requirements or with complete respiratory failure that requires intubation and ventilation will likely benefit from drainage. Other indications for drainage of the pleural space include the finding of thick pus at diagnostic thoracentesis, presence of fever and systemic illness after 5 to 7 days of therapy, presence of effusion for more than 10 days, and, in cases of toxic shock with *S aureus*, debulking disease and thus toxins.

Data are limited regarding an optimal drainage procedure; therefore, the procedure type is often based on institutional expertise, availability, and provider comfort. Options include thoracentesis, chest tube placement with or without fibrinolytics, VATS, and thoracotomy for open decortication. Randomized controlled trials in which VATS was compared to the use of a chest tube with fibrinolytics indicated that the therapies are equivalent in terms of length of stay but favored the chest tube with fibrinolytics in terms of cost and favored VATS in terms of rates of need for

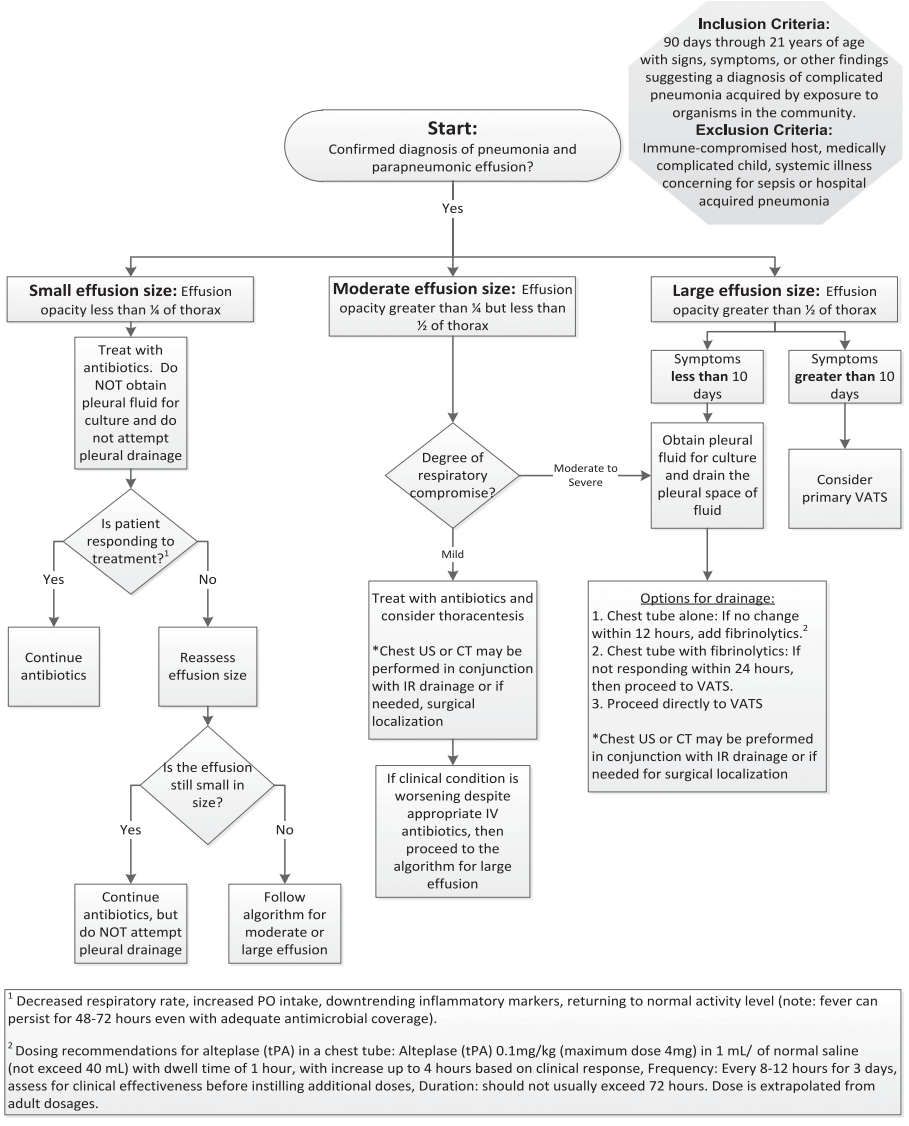

Figure 3. Management of pneumonia with parapneumonic effusion. Adapted from Bradley et al. Clinical Infectious Disease 2011 and from Complicated Community Acquired Pneumonia, Clinical Care Guidelines, Children's Hospital Colorado, updated October 11, 2016. (71) CT=computed tomography, IR=interventional radiology, IV=intravenous, PO=per os, tPA=tissue plasminogen activator, US=ultrasonography, VATS=video-assisted thoracoscopic surgery.

additional drainage procedures. (60)(61) Fibrinolytics should be considered with chest tube placement to address loculated infection and to facilitate effluent drainage. Choice of fibrinolytic is dictated in part by availability, with tissue plasminogen activator being the most commonly used in the United States. Dosages have not been fully validated in children and are variable in the literature. (60)(62) By extrapolating the adult dosages, our center uses tissue plasminogen activator of 0.1 mg/kg, given in 3 total doses (every 24 hours) with a dwell time of 1 hour (Fig 3). (6)

Lung abscesses are increasingly rare in pediatric complicated pneumonia because of increased access to care and treatment with antibiotics. They may occur as a complication within necrotizing pneumonia but can also occur in cases of more subacute scenarios. Lung abscesses are characterized by the presence of a well-defined "rim" of fibrosis around liquefaction necrosis, with or without air fluid levels. The primary parenchymal infection that leads to a lung abscess may originate hematogenously, via aspiration of oral flora, or secondary to an inhaled foreign body. Owing to their rarity in previously healthy children, lung abscesses should trigger further consideration of underlying conditions or predisposing risk factors, including aspiration (acute or chronic), foreign body, and structural abnormality, such as a pulmonary sequestration or congenital pulmonary airway malformation (formerly known as *congenital cystic adenomatoid malformation*). Immunodeficiency or chronic infection should be considered when *M tuberculosis* or endemic fungi are identified. It is difficult to differentiate lung abscess from other structurally similar complications, such as loculated pneumothorax, pneumatocele, or cavitary necrosis. Chest CT is the imaging modality of choice.

There is not strong evidence that surgical drainage of small to moderately sized abscesses improves outcomes over prolonged medical therapy alone. (63) Aspiration and culture of fluid from lung abscesses are typically reserved for patients who do not respond to appropriate antibiotics within 5 to 7 days because drainage carries risk, and most abscesses will drain spontaneously via the bronchial tree. Antibiotic treatment must often be initiated without a specimen or before identification of specific bacteria. Parenteral therapy should reflect the empirical recommendations in Fig 1, with care given to considering additional anaerobes and gram-negative organisms if aspiration is suspected as the etiologic origin of the abscess. Duration of treatment is typically 4 to 6 weeks, with at least 1 to 2 weeks of therapy after resolution of fever and until normalization of inflammatory markers. Performing repeat imaging to follow up resolution is indicated.

When lung necrosis and abscess develop near the pleural boundary, inflammation and infection can erode from the airway and enter the pleural space, creating an air leak known as a *bronchopleural fistula*. This complication is rare in pediatric pneumonia, but some single-center retrospective case reviews have indicated increasing rates associated with specific pneumococcal serotypes. (64) Care of this complication is not straightforward and requires a multispecialty approach, including surgical consultation.

Round pneumonia is a separate complication from an abscess, although also very rare. It has a distinctive radiologic pattern, described as an opaque round shape, and a study of children with round pneumonia typically demonstrated the consolidations to have well-defined borders, to be located posteriorly, and to be solitary in their distribution. Round lesions on chest radiographs should trigger consideration of a broader differential diagnosis, including fungal infection, lung abscess, and congenital or acquired pulmonary malformations such as cysts, congenital pulmonary airway malformation, or pulmonary sequestration, as well as a range of neoplasms, including lymphoma and neuroblastoma. (65) Primary pulmonary malignancies are rare in pediatrics.

Necrotizing pneumonia is an inexact term used to denote evidence of parenchymal necrosis in the lung. It is commonly a precursor for a range of complications, including lung abscess and pneumatocele. Radiologically, these changes appear as focal lucencies on chest radiographs, often with an accompanying parapneumonic effusion. CT scans, when obtained, show areas of low attenuation within the parenchyma that are attributed to liquefaction; these areas can be patchy or continuous, with an area of consolidation. Importantly, the term *necrotizing pneumonia* conveys an assessment of clinical severity out of proportion to traditional symptoms of severe pneumonia, since some of these patients progress rapidly to septic shock and respiratory failure. Necrotizing pneumonia is thought to be caused by particularly virulent bacterial strains of *S pyogenes, S pneumoniae,* or *S aureus,* particularly *S aureus* harboring Panton-Valentine leukocidin, a toxin associated with neutrophil lysis. (66) Similar to patients with lung abscess discussed earlier, most cases of necrotizing pneumonia resolve with medical treatment alone.

Antimicrobial therapy of complicated pneumonia should include coverage for *S pneumoniae* for all patients, and for very ill patients or those with influenza, therapy should include coverage for *S pyogenes* and *S aureus,* with consideration for empirical MRSA coverage. Antimicrobial agents should be narrowed as soon as possible, (67) as directed by culture results and local epidemiology (Fig 1). Two to 4 weeks of antibiotic therapy is typical for treatment of complicated pneumonia; however, there is a lack of data to support a definitive length of treatment. Length of therapy

should be determined by the clinical course and response to therapy. Parenteral antibiotics are recommended for initial therapy to optimize antimicrobial concentrations in the lung tissue and pleural fluid. The decision to transition a patient with complicated CAP to oral antibiotics is best guided by clinical response, including improved respiratory status, decreasing fever, and decreasing inflammatory markers. In a recent study, there were no differences in complications related to infection in patients treated with IV versus oral antibiotics. (61)

Severe pneumonias have other well-described associations worth mentioning that may complicate care in the acute setting. These include syndrome of inappropriate antidiuretic hormone and hemolytic-uremic syndrome (particularly with *S pneumoniae*). Another rare complication of pneumonia is empyema necessitans. This occurs when infected fluid in the chest erodes into the chest wall, causing local symptoms where the erosion occurs. Empyema necessitans is seen in more indolent infection that has gone undetected, such as with actinomycetes or mycobacteria or, rarely, inadequately treated traditional bacterial complicated pneumonia.

USE OF FOLLOW-UP RADIOLOGY

Repeat chest radiography is indicated in cases of clinical deterioration or instability after 24 to 48 hours of antibiotics. Identification of effusion or worsening infiltrate can inform decisions about broadening antibiotic coverage or consideration of pleural drainage.

In patients with a chest tube in place, standards vary from institution to institution about serial chest imaging, with some supporting daily radiographs to be acquired to be able to monitor chest tube placement, while others only repeat chest radiography in cases of clinical deterioration or possible tube malfunction.

In the outpatient realm, repeat chest radiographs are not indicated in most cases of mild, moderate, or even severe pneumonia. Because recurrent pneumonia in a specific location may suggest underlying anatomic abnormalities, chest imaging should be repeated 6 to 8 weeks after clinical resolution of pneumonia. Complete radiologic resolution of acute pneumonia occurs by 2 months in more than 90% of cases. (68) Radiographic resolution of a lung abscess and round pneumonia should be documented.

RECURRENT BACTERIAL PNEUMONIAS

Recurrent pneumonia is defined by more than 2 episodes of pneumonia in 1 year or more than 3 episodes in a lifetime. Approximately 8% of patients hospitalized for pneumonia meet these criteria. (68) Regardless of the age of the patient, recurrent pneumonia should trigger further evaluation for underlying microbiological, functional, anatomic, and chronic disease factors. (69)(70) Conducting radiologic follow-up at 2 months to distinguish persistent from recurrent pneumonias is reasonable to assist in determination of a differential diagnosis and to direct further imaging, laboratory testing, and procedural evaluation. (68)

Diagnosis of recurrent or persistent pneumonia is confirmed by means of persistent findings of opacification on chest radiographs. Further evaluation of persistent localized consolidation starts with direct visualization and sampling of the affected region by means of flexible bronchoscopy and bronchoalveolar lavage. Cytologic analysis and culture of the fluid can demonstrate persistent pathogens or suggest aspiration if a high burden of lipid-laden macrophages is seen. CT with contrast material is used to evaluate the parenchyma and distal airways. Pathologic changes such as airway bronchiectasis, cystic changes, and congenital sequestrations and infectious complications, such as cavitary abscesses or pleural effusion with loculations, can direct further evaluation and therapies.

Consolidations that persist and/or recur in the same area suggest a persistent pathogen or a focal anatomic abnormality. Persistent infectious causes include less common pathogens, such as tuberculosis, endemic fungal infections, *Actinomyces*, and nocardiosis. Focal anatomic abnormalities include obstructing lesions of the airway, including a retained foreign body, compressing lymph node or tracheal growth, compressing vascular rings or slings, and dynamic obstruction due to compressive tracheal tracheomalacia or bronchomalacia. Other focal abnormalities lead to poor clearance, such as segmental bronchiectasis, tracheal bronchus, pulmonary sequestration, or airway cyst, can lead to poor mucociliary clearance. *Right middle lobe syndrome* describes the presence of recurrent right middle lobe consolidations that likely occur because of poor collateral ventilation due to the acute angle to that lobe from the right mainstem bronchus. This lobe is more susceptible to atelectasis, aspiration, and lymph node compression.

Infiltrates that recur, but in anatomically distinct areas, invoke concern for immune defects or difficulties with airway clearance. Asthma causes recurrent atelectasis and infiltrates due to airway inflammation and mucus plugging. Associated symptoms of airway reactivity, including nighttime cough and wheeze that is worse with activity, can suggest uncontrolled asthma. Other defects and/or diseases to consider include cystic fibrosis, ciliary defects, surfactant protein defects, HIV, and congenital immune deficiencies.

A negative newborn screening test finding for cystic fibrosis should not deter the provider from pursuing a sweat chloride test. If results are positive, the provider should contact the nearest cystic fibrosis center for further evaluation. Another unusual cause to consider is recurrent bacterial seeding of the lungs in patients with cardiac defects, especially valvular disease and septal defects.

The tempo of the evaluation is dictated by the severity of the illness. For example, chronic hypoxemia, hypoventilation, weight loss, persistent fevers, anemia, leukopenia or leukocytosis, or digital clubbing would all trigger a more aggressive approach. Recurrent pneumonia evaluation can be aided by referral to specialists, including an infectious disease specialist, pulmonologist, and otolaryngologist.

DIAGNOSIS AND MANAGEMENT OF PNEUMONIA IN PATIENTS WITH NEUROMUSCULAR DISEASE

Pneumonia in patients with neuromuscular disease (including spinal muscular atrophy and Duchenne muscular dystrophy) requires additional diagnostic considerations and management recommendations. Because of persistent muscle weakness that leads to restrictive lung physiology, most patients with neuromuscular disease have decreased total lung capacity. Compounding this physiology, these patients often have impaired cough function at baseline, and bulbar weakness may increase the risk for aspiration into the lungs. Thus, these patients are at high risk for developing pneumonia in general, and it can be community acquired, hospital acquired, or health care associated. Once infected, the decreased pulmonary reserve accelerates deterioration to respiratory failure in these patients. (71)

Initial diagnosis and stabilization should include early consideration of chest radiography, electrocardiography, blood gas analysis, and assessment of electrolyte levels. Patients with spinal muscular atrophy are at risk for hypoglycemia if they receive nothing by mouth for 4 to 6 hours and should be started on IV dextrose, regardless of hydration status, if they receive nothing by mouth. Empirical antibiotic coverage includes traditional CAP coverage, but based on clinical history, risk factors, and past microbiology, may need to be expanded to cover anaerobes, gram-negative findings (including resistant gram-negative findings), and/or MRSA. A diagnostic bronchoalveolar lavage should be considered in intubated patients. Supportive care with oxygen and biphasic noninvasive ventilation is often essential, being mindful that increasing fractional index of oxygen alone or instituting continuous positive airway pressure may blunt the hypoxic respiratory drive response in the setting of chronic hypercapnia. Airway clearance regimens that include mechanical insufflation-exsufflation are important in aiding mucus clearance and airway recruitment. Admission criteria for patients with neuromuscular disease are more conservative, requiring assessment of each patient in relationship to his or her pulmonary baseline. If the patient requires continuous nasal intermittent positive pressure ventilation, new or increased oxygen requirement, or new or worsened hypercapnia or if suctioning and cough augmentation requirements are frequent, the patient should be admitted with consideration of critical care services. Consider cardiac dysfunction as either primary or secondary to respiratory distress, since many of these patients develop cardiomyopathy (particularly with Duchenne muscular dystrophy).

Summary

- On the basis of some research evidence, as well as consensus, treatment of uncomplicated community-acquired pneumonia can reasonably be achieved in 7 days or less. (43)(44)(45)
- On the basis of strong evidence, narrow-spectrum treatment is the preferred therapy in almost all settings. (6)(33)(35)
- On the basis of consensus and moderate evidence, in this era of antimicrobial resistance, efforts to obtain a specimen for pathogen identification may be beneficial.
- On the basis of strong evidence, consideration of surgical and/or procedural management of complicated pneumonia should be based on size of effusion and clinical severity. (6)(13)
- On the basis of moderate evidence, patients with recurrent pneumonia require further evaluation.
- On the basis of expert consensus, patients with a neuromuscular disorder are particularly susceptible to severe disease and more resistant pathogens and may require broader antibiotic coverage and aggressive airway clearance.

References for this article are at http://pedsinreview.aappublications.org/content/38/9/394.

Respiratory Syncytial Virus Infection and Bronchiolitis

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Practice Gaps

1. Respiratory syncytial virus (RSV) is the most common respiratory pathogen in infants and young children worldwide. Although the most effective management of this infection remains supportive care, many patients continue to be managed with therapies that lack the support of scientific evidence.
2. Although the quest for a safe and effective vaccine remains unsuccessful, the more vulnerable patients can be protected with passive prophylaxis. Because of limited clinical benefits and high costs, RSV prophylaxis should be limited to high-risk infants as directed by the most current evidence-based guidelines that, however, are not consistently followed.
3. The acute phase of this infection is often followed by episodes of wheezing that recur for months or years and usually lead to a physician diagnosis of asthma. The phenotype of post-RSV wheezing is different from atopic asthma, yet it is usually managed using the same pharmacologic therapy with often ineffective results.

Objectives

After reading this article, readers should be able to:

1. Understand the microbiology, epidemiology, pathophysiology, and clinical manifestations of RSV bronchiolitis in infants and children.
2. Know the scientific evidence relevant to prophylactic and therapeutic strategies currently available and recognize the lack of evidence concerning several pharmacologic agents commonly used in the management of bronchiolitis.
3. Be aware of alternative pharmacologic strategies currently being evaluated.
4. Learn the epidemiologic and experimental information suggesting the existence of a link between early-life infection with RSV and the subsequent development of recurrent wheezing and asthma in childhood and adolescence.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
DBPC	double-blind, placebo-controlled
FDA	Food and Drug Administration
LRTI	lower respiratory tract infection
RSV	respiratory syncytial virus

VIROLOGY

Human respiratory syncytial virus (RSV) is a single-stranded RNA virus of the Paramyxoviridae family whose genome includes 10 genes that encode 11 proteins (**Figure 1**). Two surface proteins, the F (fusion) protein and the G (attachment glycoprotein) protein, are the major viral antigens and play a critical role in the virulence of RSV. The G protein mediates RSV attachment to the host cell, after which the F protein enables fusion of the host and viral plasma membranes to permit virus passage into the host cell. The F protein also promotes the aggregation of multinucleated cells through fusion of their plasma membranes, producing the syncytia for which the virus is named and allows the transmission of virus from cell to cell. RSV has 2 distinct antigenic subtypes, A and B, which are usually present in the communities during seasonal outbreaks. It remains controversial whether subtype A is more strongly associated with severe disease.

EPIDEMIOLOGY

RSV is the most frequent cause of bronchiolitis in infants and young children and accounts in the United States alone for approximately 125,000 hospitalizations and 250 infant deaths every year. Global estimates by the World Health Organization indicate that RSV accounts overall for more than 60% of acute respiratory infections in children. Furthermore, RSV is responsible for more than 80% of lower respiratory tract infections (LRTIs) in infants younger than 1 year and annually during the peak of viral season. In summary, RSV is by far the most frequent cause of pediatric bronchiolitis and pneumonia (**Figure 2**).

Nearly all children are infected at least once by the time they are age 2 years, but peak incidence occurs between ages 2 and 3 months and corresponds to nadir concentrations of protective maternal IgG transferred to the fetus through the placenta. Seasonal outbreaks occur each year throughout the world, although onset, peak, and duration vary from one year to the next. In the United States, the annual epidemics usually begin in November, peak in January or February, and end in May.

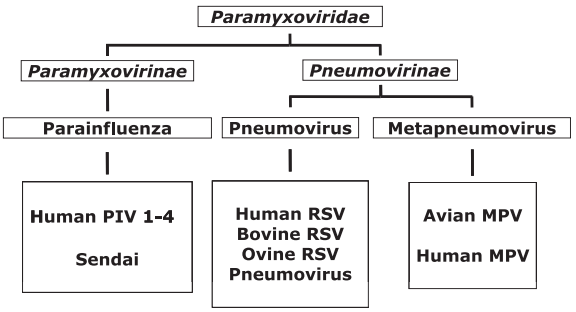

Figure 1. Respiratory syncytial virus (RSV) classification. Human RSV is an enveloped, nonsegmented, negative-strand RNA virus of the Paramyxoviridae family, genus *Pneumovirus*. The closely related *Metapneumovirus* genus was considered an exclusively avian virus until the discovery of a human strain in 2001.

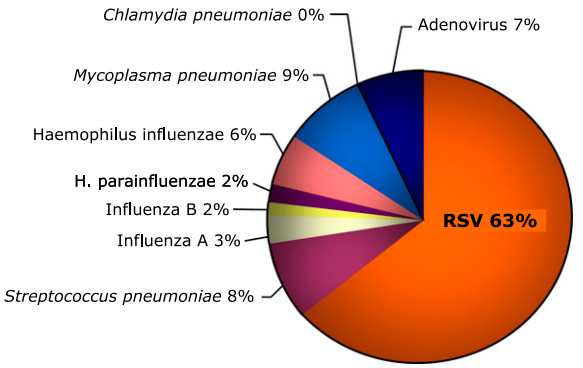

Figure 2. Etiology of acute respiratory infections in children. The World Health Organization estimates indicate that respiratory syncytial virus (RSV) accounts worldwide for more than 60% of acute respiratory infections in children and more than 80% in infants younger than 1 year and at the peak of viral season. Therefore, RSV is by far the most frequent cause of pediatric bronchiolitis and pneumonia.

However, the epidemiology of RSV differs widely across latitudes and meteorologic conditions. For example, at sites with persistently warm temperatures and high humidity, RSV activity tends to be continuous throughout the year, peaking in summer and early autumn. In temperate climates, RSV activity is maximal during winter and correlates with lower temperatures. In areas where temperatures remain colder throughout the year, RSV activity again becomes nearly continuous. Thus, RSV activity in communities is affected by both ambient temperature and absolute humidity, perhaps reflecting meteorologic combinations that allow greater stability of RSV in aerosols.

Morbidity and mortality of RSV disease are higher in premature infants and in infants with chronic lung disease (eg, bronchopulmonary dysplasia, cystic fibrosis, and interstitial lung diseases) or hemodynamically significant congenital heart disease. Because preterm infants miss, in part or completely, the third trimester window during which the placenta expresses Fc receptors mediating the transfer of maternal IgG to the fetus, they are born with reduced humoral protection against infection and reach lower nadir concentrations of maternal IgG. This is compounded by T-cell–mediated responses that are inefficient because T cells also mature primarily during the last trimester of pregnancy.

Development of bronchopulmonary dysplasia or other chronic respiratory conditions amplifies the risk of severe

infections by limiting pulmonary functional reserve, distorting airway architecture, and promoting a proinflammatory milieu. Additional risk factors for severe disease include age younger than 12 weeks, history of prematurity, male sex, crowding, lack of breastfeeding, congenital heart disease, and any immunodeficiency. Despite numerous studies that have explored whether environmental tobacco smoke exposure affects RSV morbidity, definitive evidence of this association is lacking, and its clinical significance remains controversial. Nevertheless, physicians should inquire about tobacco smoke exposure when assessing infants and children for bronchiolitis and advise caregivers about smoke cessation.

Previous infection with RSV does not convey persistent immunity even in the presence of significant antibody titers, although higher titers may attenuate the course of the disease. Consequently, subsequent infection is common, can recur within the same viral season, and occurs across all age groups. The first episodes of infection typically occur in the first 2 years after birth and tend to be the most severe because of the limited immunologic protection discussed above, smaller airway size, and unique structural and functional features of the developing respiratory tract (eg, lack of interalveolar pores and channels and different innervation patterns).

Most subsequent infections remain confined to the upper respiratory tract and run a milder course, although the illness may still progress to an LRTI, especially in elderly and immunodeficient patients, usually characterized by more severe symptoms. The clinical manifestations of RSV pneumonia in immunocompromised patients vary, depending on the extent and severity of the underlying deficit, ranging from substantial morbidity and mortality in the first 3 months after bone marrow transplantation to a usually milder course in patients with AIDS.

PATHOGENESIS AND PATHOPHYSIOLOGY

Transmission of RSV infection occurs through inoculation of the nasopharyngeal or conjunctival mucosa with respiratory secretions from infected individuals. The virus remains viable on hard surfaces for up to 6 hours, on rubber gloves for 90 minutes, and on skin for 20 minutes. This prolonged survival highlights the need for hand washing and contact precautions as an essential (and cost-effective) practice to limit the spread of infection, especially in clinic settings. The incubation period ranges from 2 to 8 days, and immunocompetent individuals can shed the virus for up to 3 weeks, although on average this is limited to approximately 8 days. However, viral shedding from immunocompromised individuals can continue for several months because intracellular replication is not effectively contained by specific cell-mediated immunity.

RSV infection starts in the nasopharyngeal epithelium but then spreads rapidly by intercellular transmission through the lower airways, reaching the terminal bronchioles, where the replication of this virus is most efficient. Direct pathologic consequences of lytic viral replication include sloughing of necrotic epithelial cells, which exposes the dense subepithelial network of nociceptive nerve fibers, forming the afferent limb for the cough reflex. The initial influx of polymorphonuclear neutrophils into the airways is rapidly replaced by predominantly lymphomononuclear infiltration of peribronchiolar tissues and increased microvascular permeability, leading to submucosal edema and swelling. Mucous secretions increase in quantity and viscosity and tend to pool because of the loss of ciliated epithelium, resulting in widespread mucous plugging.

This constellation of acute inflammatory changes that form the immediate response to exponential viral replication in the bronchioles leads to airway obstruction and air trapping, producing the classic clinical triad of polyphonic wheezing, patchy atelectasis, and bilateral hyperinflation. However, disease severity and duration are primarily a function of the immune response mounted by the host. Innate immune mechanisms provide the respiratory tract with a first barrier against the establishment of a productive infection. Subsequently, specific humoral and cell-mediated immunity play a critical role in clearing the infection and attenuating its course.

Although this response does not result in complete protection against subsequent infection, it decreases their severity. In infants, higher titers of maternally derived RSV-neutralizing antibody are associated with a much lower risk of hospitalization due to RSV, and this protective effect can be replaced or enhanced in high-risk infants by passive prophylaxis. Cytotoxic T lymphocytes are central in the control of active infection and viral clearance, which explains why immunocompromised individuals with deficient cell-mediated immunity experience more severe and prolonged RSV disease and shed the virus much longer.

CLINICAL MANIFESTATIONS

RSV infection in children almost always causes clinical manifestations, but these manifestations can vary widely in severity, depending on the patient's age, comorbidities, environmental exposures, and history of previous infections. Typically, the infection starts with signs and symptoms

of mucosal inflammation and irritation of the upper respiratory tract (congestion, rhinorrhea, and sneezing). In the next few days, the clinical status evolves with involvement of the lower respiratory tract manifested by cough and increased work of breathing with use of accessory respiratory muscles to overcome the increased resistance of obstructed airways. As noted above, many of the clinical manifestations of airway obstruction are driven by the immune response against the virus rather than by viral replication and direct cytotoxicity. Therefore, wheezing and other typical signs of bronchiolitis may be reduced or even absent in immunosuppressed patients and be replaced by rapidly evolving parenchymal infiltrates that can lead to acute respiratory distress syndrome.

Inspection reveals respiratory distress ranging from minimal to profound respiratory failure associated with a variable degree of nasal flaring and intercostal retractions. Auscultation reflects the vibration of conducting airways generated by turbulent airflow and is remarkable for a prolonged expiratory phase, diffuse polyphonic wheezing, and coarse crackles (rales) scattered throughout the lung fields. Pulse oxymetry and arterial blood gas analysis detect moderate to severe hypoxemia derived primarily from the perfusion of respiratory units that are poorly ventilated because of mucous plugging (ventilation-perfusion mismatch). Progressive carbon dioxide retention and respiratory acidosis signal the development of respiratory muscle fatigue and evolving respiratory failure that require ventilatory assistance.

Infants are usually more severely affected and may also develop lethargy, fever, poor feeding, and otitis media, whereas older children typically manifest symptoms of the upper respiratory tract but may also develop tracheobronchitis. Apnea is a well-known complication of RSV infection in infants, and its incidence is as high as 20% in infants younger than 6 months who require hospitalization. When present, apnea usually is an early event that precedes lower respiratory tract signs and symptoms, suggesting the involvement of reflex neural activity triggered in the upper airways. The highest incidence of apnea occurs in premature infants and in infants younger than 1 month, probably because of the relative immaturity of ventilatory control. In most cases, however, apnea is self-limited and does not recur with subsequent infections.

The diagnosis of acute bronchiolitis should be based exclusively on the history and physical examination findings and does not require radiographic or laboratory studies. The specific cause can be confirmed by antigen detection tests, currently being replaced by more sensitive polymerase chain reaction–based assays. Arguably, this step in not essential because, especially during the epidemic peak and in the first year after birth, RSV is responsible for most cases of bronchiolitis and other pathogens are much less common. However, confirming the viral origin strengthens the rationale for withholding therapies known to be ineffective and provides prognostic clues concerning complications, such as recurrent wheezing and asthma, based on robust epidemiologic data.

Correct etiologic diagnosis is also important to rule out rare conditions that could be worsened by the management commonly used for bronchiolitis. For example, infants with dilated cardiomyopathy and congestive heart failure may present with symptoms of wheezing that mimic an acute respiratory infection, but these patients are at risk of developing supraventricular tachycardia and even cardiopulmonary collapse after administration of β-agonist agents. In cases of suspected cardiac disease, chest radiography will reveal cardiomegaly, suggesting a different diagnosis and therapy, and thereby might avoid significant complications or even death.

Other laboratory and imaging studies also add little information, although it is advisable to determine the complete and differential blood cell counts and C-reactive protein level to assess the risk of bacterial superinfection in febrile children, as well as electrolyte serum concentrations to monitor

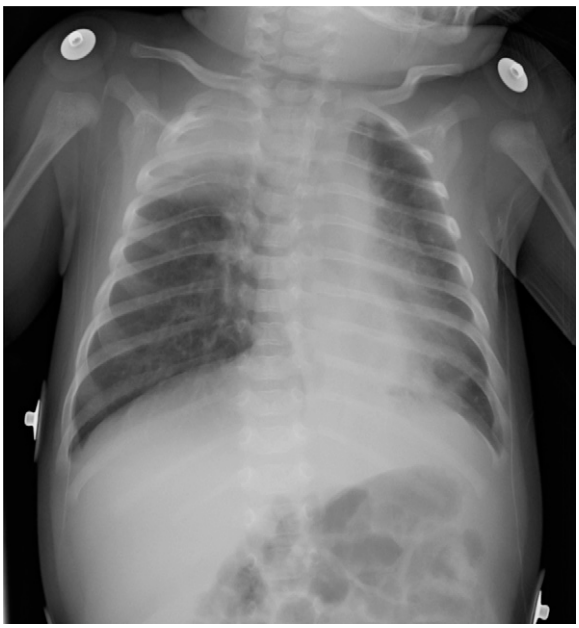

Figure 3. Clinical manifestations of respiratory syncytial virus (RSV). Chest radiography performed in a child with RSV bronchiolitis revealed bilateral hyperinflation from air trapping, patchy atelectasis from airway plugging, and peribronchial thickening from lymphomonocytic infiltration. Patients with severe disease may also have features more consistent with pneumonia, with areas of interstitial parenchymal infiltration.

hydration status and electrolyte imbalance. If chest radiography is performed, findings typically include bilateral hyperinflation, patchy atelectasis, and peribronchial thickening, but patients with severe lower respiratory tract involvement have radiologic features more consistent with pneumonia and areas of interstitial parenchymal infiltration (**Figure 3**).

THERAPY

Supportive Care

Most infants with RSV infection develop a mild, self-limited illness, which is usually managed in outpatient settings but still requires close follow-up with special attention to respiratory distress, oxygen requirement, and hydration. Those infants with difficulty feeding, pronounced respiratory distress, or need for supplemental oxygen require hospital admission for more aggressive management and monitoring. Regardless of the setting in which the patient is treated, the mainstay of therapy remains supportive care, which includes respiratory support combined with appropriate fluid and nutrition management (**Figure 4**).

Nasal obstruction is a common problem in young infants who are obligate nose breathers and often improves significantly after nasal toilet with saline drops and a suction bulb. Chest physiotherapy is often provided in an effort to mobilize secretions and reexpand atelectatic segments, but a recent Cochrane systematic review found no evidence to support its use, which, combined with the unnecessarily increased hospitalization costs, should discourage this practice.

Children with oxygen saturations of 90% or less should receive warm, humidified oxygen. Infants with hypoxemia refractory to supplemental oxygen, persistent respiratory distress, or evolving respiratory failure require either noninvasive support with nasal continuous positive airway pressure or endotracheal intubation. Positive pressure mechanical ventilation has been used for decades in the management of infants with severe RSV bronchiolitis and is probably one of the most important factors that lead to the progressive decrease in mortality. A few infants with particularly severe disease may require escalation of mechanical ventilation to high-frequency oscillatory ventilation or extracorporeal membrane oxygenation.

Infants hospitalized with RSV bronchiolitis often have decreased nutritional intake due to respiratory distress and tachypnea with increased insensible losses and will need fluid and nutritional support. Continued oral feeding in the presence of significant tachypnea and respiratory distress is known to increase the risk of aspiration. Indeed, aspiration has been revealed with the use of barium contrast in a significant proportion of infants hospitalized with RSV bronchiolitis. Thus, in patients who are unable to tolerate oral feeds, adequate fluid intake and nutrition should be maintained by placement of a nasogastric or orogastric feeding tube or with parenteral fluids when enteral nutrition is deemed unsafe.

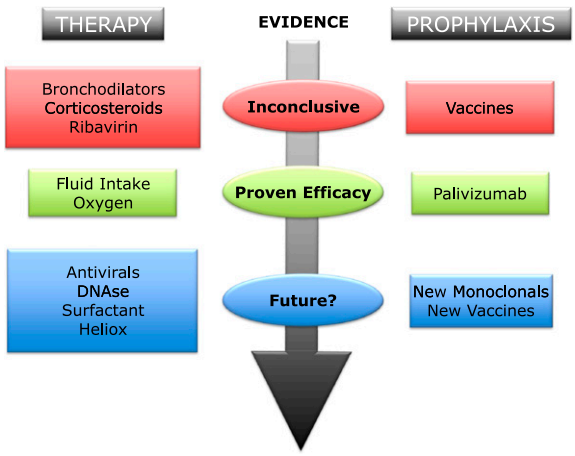

Figure 4. Evidence-based management of bronchiolitis. Passive prophylaxis is a safe and effective way of protecting infants at risk for severe respiratory syncytial virus (RSV) disease but is not cost-efficient. Once the infection is established, the mainstay of current therapy remains supportive care because no solid scientific evidence supporting the use of any conventional or experimental pharmacologic agent currently exists. For the future, promising antiviral molecules and new-generation humanized monoclonal antibodies are being investigated, and structural biology may overcome the challenges that have so far prevented the development of a safe and effective RSV vaccine.

Pharmacologic Therapy

Despite relentless attempts to identify pharmacologic strategies to improve the clinical course and outcomes of this infection, the most effective management remains limited to the supportive care measures discussed above. There is no solid scientific evidence supporting the use of any pharmacologic agent currently available.

Bronchodilators. Albuterol does not provide consistent benefit in the treatment of RSV infection and should not be administered to infants and children diagnosed as having bronchiolitis. A brief trial with objective evaluation of the response may be warranted, but this therapy should be discontinued if no improvement occurs because of the significant adverse effects, including tachycardia, tremor, hypokalemia, and hyperglycemia. These adverse effects can be amplified and become life-threatening in patients with underlying lung or heart disease, also due to the interaction with other commonly used therapies (eg, diuretics).

Other inhaled selective β-agonists, such as levalbuterol, have no demonstrable advantage over albuterol in humans despite preliminary data in rodent models that suggest

potential benefits. Epinephrine does not provide consistent benefit in the inpatient setting, and although some studies suggest that it may produce a modest improvement in the outpatient setting, it is not deemed safe for use at home or other settings where cardiorespiratory monitoring is not available. Oral or parenteral adrenergic agonists have no advantages over nebulized ones but have much stronger adverse effects that contraindicate their use in any obstructive airway disease, including bronchiolitis. Finally, there is no evidence supporting the use of anticholinergic agents, such as atropine or any of its synthetic derivatives, which may also have significant untoward effects by predisposing patients to more extensive mucous plugging.

Hypertonic Saline. Nebulization of 3% saline improves mucociliary clearance and is increasingly being used in airway diseases that involve mucous plugging (eg, cystic fibrosis). It has also been reported to reduce length of hospital stay and provide symptomatic relief in patients with bronchiolitis, but its use remains controversial. In particular, it is not effective in reducing hospitalization when used in emergency settings. Therefore, on the basis of current evidence, the administration of hypertonic saline for bronchiolitis should be limited to hospitalized infant and children.

Corticosteroids. Neither systemic nor inhaled corticosteroids have consistent benefit in the treatment of acute RSV disease or in the prevention of post-RSV wheezing. In particular, a systematic review of 13 trials of corticosteroid therapy in 1,198 children with viral wheezing ages 0 to 30 months concluded that this therapy lacks any significant clinical benefit compared with placebo and is not indicated for this patient group. The findings of this meta-analysis have been complemented by a number of more recent individual studies that have reached more or less the same conclusions.

Another area of concern derives from safety considerations. In fact, viral bronchiolitis typically occurs during the first year after birth and coincides with a critical phase of rapid lung growth. The safety of corticosteroids during this developmental window is virtually unknown, and corticosteroids are not approved by the Food and Drug Administration (FDA) for use in the treatment of bronchiolitis or asthma in the first year after birth. Therefore, on the basis of current and extensive scientific evidence, corticosteroids are not recommended for routine use in the treatment of acute bronchiolitis.

It has been argued that virus-induced wheezing in infants and young children could be the early manifestation of persistent asthma and therefore warrant the use of corticosteroids for the secondary prevention and control of asthma. However, in general young children without an atopic phenotype who wheeze in response to viral infections show a poor response to corticosteroids, and even children who will ultimately develop chronic asthma are usually unresponsive to this therapy when they develop virus-induced wheezing during their first years after birth.

Antimicrobials. The only antiviral agent ever licensed by the FDA for the therapy of severe RSV infections is ribavirin, a synthetic nucleoside analog with broad in vitro virustatic activity. Unfortunately, by the time the infection manifests clinically in vivo, most of the viral load has already been cleared, and the disease process is driven primarily by inflammatory mechanisms largely independent from viral replication. After some initial encouraging data from industry-sponsored studies, a series of randomized trials were unable to demonstrate any short- or long-term improvement in the clinical course of bronchiolitis, leading to a rapid decline and virtual disappearance of ribavirin use in this setting. Therefore, inhaled ribavirin is no longer recommended for routine treatment of RSV infection, although it may be considered in select immunocompromised individuals, who can continue to shed virus for several months because replication is not limited by host defenses.

Antibiotics should be used in patients with bronchiolitis only when specific evidence of coexistent bacterial infection is present. Such coinfections are uncommon, perhaps with the exception of bacterial otitis media that can be managed with oral antibiotics no differently than in the absence of bronchiolitis.

Experimental Agents. A variety of other experimental therapeutic interventions has been tested, but none have been approved by, or even submitted to, the FDA, and currently the evidence supporting clinical use of any of them is largely insufficient. Starting with aerosol-delivered drugs, DNAse does not provide consistent benefit in the treatment of RSV infection, and although neutrophils, the primary source of extracellular DNA, are indeed recruited in the airways during the early stage of the infection, they are not predominant in RSV-infected airways as they are in cystic fibrosis, which remains the only accepted indication for this therapy. Surfactant and Heliox may provide some benefit in the treatment of this infection, but again the available data are far from conclusive.

Concerning oral drugs, antileukotrienes used during the acute phase of RSV bronchiolitis improve postbronchiolitis respiratory symptoms, especially in younger patients with high urinary leukotriene E_4 levels. However, a large, multicenter, randomized, double blind, placebo-controlled (DBPC) trial with montelukast did not find statistically significant clinical improvement. Post hoc analysis of data

collected during this trial revealed that children with persistent respiratory symptoms after the acute phase of the infection may indeed benefit from montelukast, but the manufacturer (Merck & Co) is no longer pursuing this indication. We have elected to not include in this review the extensive pipeline of antiviral compounds currently being developed because they are not likely to become available for clinical use in the foreseeable future.

PREVENTION

Disinfection with alcohol-based rubs and hand washing with alcohol-based rubs or soap and water are highly effective in reducing the spread of RSV, and it is invaluable in preventing nosocomial infections. The use of gloves and gowns can help in limiting transmission, but the use of masks is controversial because RSV is mostly transmitted by direct contact with infected secretions and rarely by aerosolization. Our own data obtained with air-sampling devices provided by the National Institute of Occupational Safety and Health have confirmed that it is rare to detect airborne RSV around infected infants (G.P., unpublished data, 2014). This observation, combined with the mounting efforts to contain health care costs through evidence-based practices, prevents us from recommending the use of masks to limit RSV transmission.

Active Prophylaxis

No vaccine exists today for active prophylaxis against RSV. A formalin-inactivated vaccine marketed in the United States in the 1960s had to be withdrawn because, in addition to being poorly immunogenic, it predisposed children to aberrant T_H2-type immune responses and life-threatening disease on subsequent exposure to wild-type virus. Since then, a vast array of experimental approaches, ranging from purified capsid proteins to attenuated or inactivated virus, have failed to deliver a safe and effective vaccine. Only recently has new hope been sparked by the use of cutting-edge structural biology to engineer a stabilized and customized version of the RSV surface F protein (immunogen) that binds highly protective antibodies and triggers a potent RSV-specific neutralizing response when injected into animals.

Passive Prophylaxis

Perhaps the most important success in the war against RSV so far has been the development of safe and effective passive prophylaxis, first with polyclonal intravenous immunoglobulin and later with monoclonal antibodies for intramuscular administration. Palivizumab is a humanized IgG1 monoclonal antibody developed by MedImmune Inc and licensed by the FDA since 1998 for the prophylaxis of children at high risk for severe RSV disease. With this technology, murine-derived sequences complementary to the A antigenic site of the RSV F protein were grafted into a human IgG frame, resulting in a protein that is minimally immunogenic.

Palivizumab is administered monthly during the RSV season as an intramuscular dose of 15 mg/kg, which has consistently had an excellent safety profile. America Academy of Pediatrics (AAP) guidelines providing a better definition of high risk for severe RSV disease were originally published a few months after FDA approval and have been subsequently revised 4 times to account for new evidence from postmarketing studies and to balance the limited clinical benefits with the high costs of this expensive biological agent (currently approximately $3,000 per vial). The most recent AAP Policy Statement, published in 2014 to replace the recommendations found in the 2012 *Red Book* and in the 2006 AAP guidelines for the diagnosis and management of bronchiolitis, is significantly more restrictive than the previous revisions (**Table 1**). (1)

Palivizumab prophylaxis with a maximum of 5 monthly doses is now recommended only in the first year after birth for otherwise healthy infants born before 29 weeks' gestation and for infants born before 32 weeks' gestation with chronic lung disease of prematurity defined as a requirement for supplemental oxygen for at least 28 days after birth. Prophylaxis is no longer recommended in the second year after birth, except for infants with chronic lung disease of prematurity still requiring oxygen, corticosteroids, or diuretics. Palivizumab prophylaxis should be discontinued after a breakthrough RSV hospitalization because the likelihood of a second RSV hospitalization in the same season is low. Palivizumab should be considered also for children with hemodynamically significant congenital heart defects, profound immunodeficiency, and pulmonary or neuromuscular diseases that impair airway clearance, but no formal recommendation was made for patients with Down syndrome or cystic fibrosis because of insufficient data.

As shown in preclinical studies in cotton rats, palivizumab provides optimal protection with blood levels above 40 μg/mL. Unfortunately, by using the recommended dosage, trough concentrations after the first monthly injection decrease below the protective level in more than half of the patients. Subsequently, trough levels increase after each monthly injection because of progressive accumulation. This finding explains why almost half of all breakthrough RSV hospitalizations in infants receiving prophylaxis occur after the first injection, whereas less than one-third occur

TABLE 1. **Current American Academy of Pediatrics Guidance for RSV Prophylaxis (1)**

Prophylaxis (palivizumab, 15 mg/kg IM, for a maximum of 5 monthly doses) is recommended for:
1. Infants born at <29 weeks 0 days of gestation without chronic lung disease of prematurity who are younger than 12 months at the onset of RSV season.
2. Infants with chronic lung disease of prematurity younger than 24 months who continue to require medical therapy within 6 months of the onset of RSV season.
Prophylaxis may be considered for:
1. Infants younger than 12 months with hemodynamically significant heart disease or children younger than 24 months who undergo cardiac transplantation during RSV season.
2. Infants younger than 12 months with airway abnormalities or neuromuscular disorder impairing cough.
3. Children younger than 24 months old severely immunocompromised during RSV season.
Prophylaxis is not recommended for:
1. Infants born at ≥29 weeks 0 days of gestation without chronic lung disease.
2. Infants with chronic lung disease of prematurity 12 months or older who no longer require medical therapy.
3. Children who experience a breakthrough RSV hospitalization while taking palivizumab.
4. Children with Down syndrome or cystic fibrosis.
5. Children exposed to RSV in a health care facility.
Additional recommendations
• Careful hand hygiene.
• Breastfeeding.
• Elimination of tobacco smoke exposure.
• Avoidance of crowded environments.
• Limitation of group daycare activities.

IM=intramuscular; RSV=respiratory syncytial virus.

after the first 2 injections. Furthermore, palivizumab dosage is not sufficient to reach protective levels in the nasal mucosa and therefore does not prevent infection of the upper airways or middle ear.

To address these limitations, a second-generation IgG1 monoclonal antibody (motavizumab) was synthesized based on computer modeling, studied in a variety of preclinical models, and tested clinically up to a large, multicenter phase 3 trial. The new monoclonal antibody had 70-fold higher affinity for the RSV F protein and was fully humanized. However, the FDA Advisory Committee voted not to recommend approval of motavizumab, justifying this decision based on questionable evidence that the new antibody provided additional benefit compared with palivizumab (nonsuperiority) and on concerns about the rare (2%–3%) but statistically significant increase in serious adverse events that involve the skin of infants.

PROGNOSIS

In general, RSV bronchiolitis is a self-limiting disease with excellent long-term prognosis. However, the existence of a causative relationship between RSV infection in infancy and the inception of childhood asthma has been debated for decades. There is certainly an increased risk of subsequent wheezing in children who have had RSV infection in early life, especially if the primary infection was severe enough to warrant hospitalization, but the question remains whether RSV is indeed a causative factor or rather a simple marker or trigger of a preexisting intrinsic predisposition to develop asthma.

Prospective epidemiologic studies published in the past 2 decades by Sigurs et al and Stein et al, among others, collectively suggest a 20% to 40% likelihood of recurrent asthma-like episodes after RSV LRTI in infancy. There is also general consensus that a nonatopic wheezing phenotype heralded by early RSV infections is often less responsive to corticosteroid therapy and usually resolves before adolescence. This information can be summarized in a model of asthma pathogenesis in which a genetic predisposition inherited from parents is not necessary or sufficient for the manifestation of this disease in childhood, whereas early respiratory infections, especially if severe and driven by specific viral pathogens, not only can lead to recurrent childhood wheezing even in the absence of genetic predisposition but also can amplify the risk deriving from such predisposition.

Nevertheless, epidemiologic studies are not suitable to resolve whether early-life RSV LRTIs are truly causal for subsequent asthma or more simply precipitate wheezing in children already predisposed because of their genetic or epigenetic makeup. Only carefully randomized controlled trials with specific prophylaxis can conclusively determine whether preventing or delaying the first RSV infection lessens the incidence and/or severity of asthma later in life. This is the major contribution of a recent industry-sponsored, multicenter, randomized DBPC trial by Blanken and coworkers investigating the causal role of RSV infection in the pathogenesis of wheezing illness during the first year after birth. This trial included 429 otherwise healthy infants born at 33 to 35 weeks'

gestational age, who were randomized to receive either monthly palivizumab injections or placebo during the RSV season. The primary end point was the total number of parent-reported wheezing days in the first year after birth. Consistent with previous nonrandomized data, RSV prophylaxis resulted in a relative reduction of 61% in the total number of wheezing days during the first year after birth and a statistically significant decrease in the proportion of infants with recurrent wheeze, regardless of whether there was a family history of atopy.

The data published so far provide robust preliminary evidence that RSV infection is an important mechanism in the pathogenesis of recurrent wheezing during the first years after birth. However, they are still limited to preterm children, who are at higher risk for recurrent episodes of wheezing because of intrinsic hyperreactivity and immaturity of their airways, and therefore cannot be generalized to healthy term infants, who constitute most patients who develop bronchiolitis and asthma. Thus, before a formal recommendation can be made concerning large-scale RSV prophylaxis to reduce the incidence of postviral wheeze in childhood, it will be essential to conduct independently funded, randomized, DBPC trials in large samples that include full-term infants.

Once these data are available, it will also become necessary to recalculate the clinical benefits and cost-effectiveness of palivizumab prophylaxis, which continue to be the most controversial aspects of its use. As pressures to reduce the unsustainable costs of health care continue to mount and value-based care becomes the standard model to follow, long-term cost-benefit analysis will be a predominant force shaping the use of biological agents in standard clinical protocols. Current analyses overwhelmingly argue that palivizumab is not cost-effective for the prevention of bronchiolitis, but this might change rapidly if rigorous evidence supports the notion that protection against RSV reduces the ever-growing direct and indirect costs of the asthma epidemic in industrialized countries.

Summary

- On the basis of strong research evidence, respiratory syncytial virus (RSV) is the most frequent cause of bronchiolitis and pneumonia in infants and young children and a source of significant morbidity, mortality, and financial burden worldwide. (2)
- On the basis of some research evidence and consensus, transmission occurs through inoculation of the nasopharyngeal or conjunctival mucosa with respiratory secretions from infected individuals. Viral shedding persists for approximately 1 week but can be significantly prolonged in immunocompromised individuals. (3)
- On the basis of expert opinion, infants with RSV infection typically present with upper respiratory tract symptoms that frequently progress to involve the lower respiratory tract with cough, wheeze, and increased work of breathing. Chest radiography typically reveals hyperinflation, patchy infiltrates, and atelectasis. Apnea can be the presenting manifestation, especially in young infants. The diagnosis of RSV bronchiolitis should be based on history and physical examination and does not require radiographic or laboratory studies.
- On the basis of expert opinion, supportive care is the mainstay of therapy for RSV disease and is directed at ensuring adequate oxygenation, improving respiratory toilet, and meeting fluid and nutrition requirements. Chest physiotherapy should not be used. Severe respiratory failure requires mechanical ventilatory support and occasionally high-frequency oscillatory ventilation or extracorporeal membrane oxygenation.
- Adrenergic α- and β-agonists do not provide consistent benefit in the treatment of RSV infection. Similarly, neither systemic nor inhaled corticosteroids have been found to provide clear advantages in this setting. Therefore, these pharmacologic agents should not be used in infants and children diagnosed as having RSV bronchiolitis. Hypertonic saline may be used in hospitalized patients but not in the emergency setting.
- On the basis of some research evidence and consensus, the antiviral drug ribavirin is also not recommended for routine treatment of RSV infection but may be considered in select immunocompromised individuals. Antibiotics should not be used in infants and children diagnosed as having RSV bronchiolitis, unless there is evidence or suspicion of a concomitant bacterial infection. (4)(5)(6)
- On the basis of strong research evidence, hand washing or disinfection by all caregivers and contact isolation of patients are highly effective in preventing the spread of RSV infection. The humanized monoclonal antibody palivizumab is a safe option for passive RSV prophylaxis, but its use should be limited to infants at high risk for severe disease because of limited clinical benefits and high costs. (7)
- On the basis of some research evidence, solid epidemiologic data suggest that early RSV bronchiolitis predisposes patients to recurrent wheezing and asthma during the first decade after birth. This hypothesis has been confirmed recently by a randomized double-blind, placebo-controlled study indicating that palivizumab significantly reduces the frequency of wheezing in infancy. However, this evidence is still limited to prematurely born infants and cannot be generalized yet to otherwise healthy children born at full term. (8)(9)(10)

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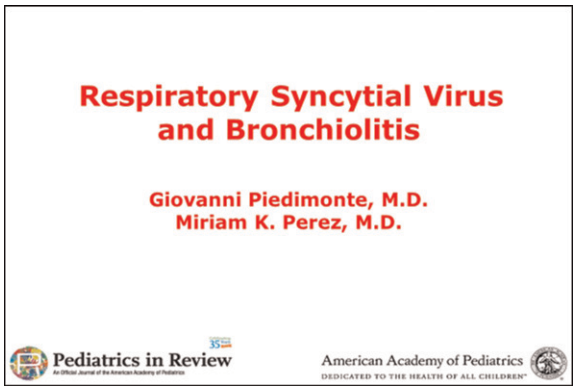
To view PowerPoint slides that accompany this article, visit http://pedsinreview.aappublications.org and click on the Data Supplement for this article.



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Parent Resources from the AAP at HealthyChildren.org

- English: http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Protecting-Your-Baby-from-RSV.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/chest-lungs/paginas/protecting-your-baby-from-rsv.aspx
- English: http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Respiratory-Syncytial-Virus-RSV.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/chest-lungs/Paginas/Respiratory-Syncytial-Virus-RSV.aspx
- English: http://www.healthychildren.org/English/health-issues/conditions/chest-lungs/Pages/Bronchiolitis.aspx
- Spanish: http://www.healthychildren.org/spanish/health-issues/conditions/chest-lungs/Paginas/Bronchiolitis.aspx

Pneumonia and Bronchiolitis Quiz

1. Worldwide, community acquired pneumonia accounts for **15%** of deaths in children younger than 5 years old.

2. Worldwide, **Respiratory Syncytial Virus** is the most common respiratory pathogen and the most frequent cause of bronchiolitis and pneumonia in infants and children.
   During peak respiratory illness season, RSV accounts for more than 60% of acute respiratory infections in children and more than 80% of acute respiratory infections in infants younger than 1 year old.

3. Best strategies for preventing pneumonia and bronchiolitis:
   Disinfection and handwashing with alcohol-based rubs, handwashing with soap and water, immunization against S. pneumoniae, H. flu, and influenza.

4. List 3 possible complications from pneumonia:
   Pleural effusion, empyema, pneumatocele, necrotizing pneumonia, lung abscess

5. TRUE/**FALSE** : Definitive identification of bacterial etiologies in CAP is possible most of the time due to newer PCR and antigen studies. Lack of primary lower tract samples continues to impede identification of specific etiologic organisms in most cases of CAP. Organisms identified in the upper respiratory tract do not definitively correlate with lower tract disease.

6. Recommended first line outpatient therapy for uncomplicated CAP includes which of the following?
   a. amoxicillin 80-90 mg/kg/day div bid for 10 days
   b. cefdinir 14 mg/kg/day for 7 days
   c. azithromycin 10 mg/kg load followed by 5 mg/kg for days 2-5
   d. **amoxicillin 80-90 mg/kg/day div tid for 7 days** -- shorter dosing interval increases killing time, unlike ear fluid, antibiotic does not concentrate in the serum. 10 days of treatment is no more effective than a seven day course in uncomplicated CAP.

7. Name 3 reasons why it is presumed that pneumonia infections peak in the winter months.
   a. indoor crowding leading to enhanced droplet transmission
   b. impaired mucociliary clearance
   c. peak of viral infections

Pneumonia and Bronchiolitis Cases

Case 1: A mother brings 2 year old son Isaac into your office for his annual well-child check. During the visit, she also mentions that Isaac has had a runny nose and cough for the past few days. She noticed last night and this morning that he seemed warm to the touch, but she didn't take his temperature. You look at his vital signs and note a respiratory rate of 26 with a pulse oximetry reading of 96% and a temperature of 100.9.

What else do you want to know?

- PMHx: Born at term, no chronic medical problems. Not on any medications. No prior hospitalizations; no prior ER visits for wheezing or respiratory distress.
- Immunizations: up to date, including recent flu shot
- SocHx: In daycare, older siblings at home with upper respiratory infections

Isaac is non-toxic appearing, but doesn't appear as active as you've seen him in other visits. You note some mild rhinorrhea, an intermittent cough, and diffuse faint end-expiratory wheezing.

What do you think is going on with Isaac? What are the signs/symptoms typical of this diagnosis?

Most likely viral pneumonia vs. bronchiolitis.

Signs & Symptoms: Fever, cough, tachypnea, increased work of breathing, hypoxia, crackles, retractions, rhonchi, nasal flaring, wheezing. Upper lobe pneumonias may present with radiating neck pain, while lower lobe pneumonias may present as vague abdominal pain.

You explain to Isaac's mom that you think Isaac likely has viral lower respiratory infection. She asks you whether or not he needs a chest x-ray to look for pneumonia, and if Isaac has to be admitted to the hospital.

What do you tell her?

Isaac's clinical presentation gives us all the information we need. He is currently mildly ill. A chest x-ray is unlikely to help differentiate viral pneumonia and bronchiolitis. He doesn't need a chest x-ray, nor does he need to be admitted to the hospital. He should have close outpatient follow-up.

What kind of "return to care" precautions do you give Isaac's mom?

If Isaac starts having trouble breathing, looks like he's working hard to breathe or breathing too fast, isn't able to stay hydrated, starts running high fevers, or isn't improving over the next few days, bring him back to clinic (or the ER if it's after hours).

Isaac's mom thanks you for your advice. On the way out the door, she asks if Isaac can still receive his 4 year old immunizations today in light of his illness.

What do you tell her?

There is good evidence that all immunizations are safe in children with mild acute illness and low grade fever. However, if significant lower respiratory tract disease is present, most would hold off on the immunizations, just because you don't want immunization adverse effects (rare, but severe allergic rxn for example) to cloud or worsen the clinical picture. In this case, immunize.

Case 2: Dad brings 3 year old Rebecca for an acute visit today because she's had a cough and runny nose for the past few days, but now has developed a fever and seems to be breathing faster than normal. She has an unremarkable past medical history: born at term, no hospitalizations, and takes no routine medications. Her vital signs are as follows: T 102.6, RR 38, HR 135, BP 92/64, SpO2 90% on room air. Physical exam is remarkable for a fussy-appearing child with increased work of breathing, tachypnea, suprasternal and supraclavicular retractions, and crackles at the left lower lung base.

What else would you like to know?

-Immunization status
-Ability to take PO (vomiting?)
-Hydration status
-Any recent antibiotic usage?

Dad says that she just hasn't been herself the past couple of days. She's not really eating much, has vomited 3 times in the past 24hrs, and is drinking sips of water occasionally. She only had 2 wet diapers yesterday, and her diaper when she got up this morning was barely damp. Her immunizations are up to date for her age, including the flu vaccine, and she hasn't ever had antibiotics before.

What do you do now?

Take her to the treatment room for supplemental oxygen and iv placement and alert your staff. Call the ward team for admission due to her increased work of breathing, tachypnea, hypoxia, likely inability to tolerate oral antibiotics, and IV fluids.

Lucky for you, you have ward call tonight, so a perfect opportunity for continuity of care with Rebecca! You decide to walk Rebecca and her Dad up to the ward to get settled and conduct the all-important IPASS handoff with the outgoing team.

What would you like to do with Rebecca on the ward? What kind of antibiotics are you going to start her on?

-IV fluids (bolus NS 20ml/kg due to dehydration, and then start maintenance fluids with D5NS)
-Ampicillin **(150-400 mg/kg/day div q6h**)*FIRST LINE THERAPY FOR CAP*
-ceftriaxone if PCN allergic, amp/sulbactam if H. flu or M. catarrhalis suspected, vanc or clinda if S. aureus suspected
-Supplemental oxygen
-CXR
-Labs (CBC with differential, RFP, blood cultures, RSV/Flu)
    ** CRP/ESR can be obtained to judge the response to treatment if desired, but clinical improvement should suffice*

What do you expect to see on the chest x-ray?

-Can be anything from nothing to a consolidated infiltrate in the left lower lobe.
    * Possibly nothing on the CXR because radiographic findings can lag behind the clinical picture for up to 72hrs, and due to her dehydration, an infiltrate may not be present initially.

Rebecca is started on 2L via nasal cannula on admission to the ward. She is started on appropriate antibiotics and does well overnight. You find in her the play room the following morning. After 24 hours on antibiotics, she is still febrile. Her respiratory rate is approaching normal and she is taking fluids po. She is able to be weaned off IV fluids the following day, and manages to spend the next night off of supplemental oxygen. Her discharge temperature is 101 F. **Can she go home?**

Yes. Patients with pneumonia may remain febrile for more than 24-48 hours after antibiotics are started. Fever should generally be trending down and other signs of improvement should be present.

What antibiotic should she go home on?
High-dose Amoxicillin divided tid to complete a 7 day course

> ** This is likely Pneumococcal pneumonia. Classically, children have fever >101, tachypnea, appear ill, have a round opacity on CXR, and have WBC > 20,000.*

She follows up 2 days after discharge (currently on day 5 of antibiotics) with you in clinic. She's back to her normal self per Dad, afebrile since leaving the hospital, eating/drinking well, no respiratory distress, and playing with her brothers. Dad asks you if she needs a repeat CXR at some point to make sure if the pneumonia is gone. He also wants to know if she needs to finish the last 2 days of antibiotics since she's back to her baseline.

What do you tell him?
Finish the antibiotics (?) -- probably best to stick to the initial plan, although some studies have shown 3 and 5 day courses to be equally effective in non severe CAP. Shorter courses may mitigate resistance, decrease side effects, and improve compli0ance.

As this was her first pneumonia, and no significant PMHx to speak of, she doesn't require a film now (or in 6 weeks) to confirm resolution of the infiltrate. Follow-up films are done in kids with repeated bouts of pneumonia.

Pneumonia Board Review

1. During teaching rounds, the pediatric ward resident reports on a 4-month-old circumcised male infant who was admitted to the pediatric ward for fever that morning. The infant is now afebrile and has had respiratory rates of 40 breaths/min while sleeping and greater than 60 breaths/min when awake. The infant has a soft, flat fontanelle on physical examination and is not irritable. The only diagnostic studies obtained on admission were a urinalysis and complete blood count, the results of which were normal, except for a white blood cell count of 16.0.

Of the following, the MOST appropriate next step is
A. administration of 100 mL normal saline
B. chest radiography
C. lumbar puncture
D. reassurance of the resident that this represents normal respiratory variation
E. urine culture

Respiratory rates vary across a relatively wide range in pediatric patients, depending on factors such as age and activity status. Therefore, strict definitions of tachypnea and bradypnea are difficult to determine and always must be considered in association with other factors such as current clinical status and individual history. Because tachypnea is a sensitive indicator of lower airway disease, patients who have elevated respiratory rates deserve a clinical evaluation in the context of other associated symptoms.

The tachypnea, history of fever, and elevated white blood cell count described for the boy in the vignette warrant chest radiography. Although lumbar puncture and a urine culture often are indicated to evaluate infants who have fever, the elevated respiratory rate combined with reassuring neurologic examination results and normal urinalysis make pneumonia a more likely diagnosis. Administration of a normal saline bolus would not be expected to improve the abnormal respiratory rate.

2. A 16 year-old girl presents with a 4-day history of fever, chills, nonproductive cough, and sore throat and a maculopapular truncal rash. On physical examination, she is well appearing. Her temperature is 39.1, her respiratory rate is 24 breaths/min, and her pulse rate is 76/min. Examination of the girl's head, eyes, ears, nose, and throat reveals an erythematous pharynx without exudates. Her neck is supple without lymphadenopathy. Respiratory auscultation reveals scattered crackles in her lungs, and cardiac auscultation shows no murmur, rub, or gallop. Her abdomen is without organomegaly, her extremities are without lesions, and results of her neurologic examination are within reference range. There is a pink maculopapular rash primarily on her trunk. You obtain a chest radiograph.

Of the following, the BEST test for confirming the cause of this child's pneumonia is
A. blood culture
B. cold agglutins
C. nasopharyngeal aspirate for viral antigens
D. sputum Gram stain and culure
E. throat swab for mycoplasma polymerase chain reaction

The combination of pharyngitis, nonproductive cough, chills, scattered rales, and skin rash in conjunction with the girl's age and the presence of bilateral infiltrates on chest radiograph is typical of symptomatic Mycoplasma pneumonia infection. Detection of mycoplasma DNA by polymerase chain reaction on throat swab specimens has recently been demonstrated to be a sensitive and specific method for diagnosing M pneumonia respiratory infections. The test is becoming increasingly clinically available. If

not available, mycoplasma IgG and IgM serology can be obtained. Routine isolation of the organism is not readily available.

It is unlikely that the girl in the vignette has "typical" bacterial pneumonia, such as caused by Streptococcus pneumoniae. Additionally, bacteremia is unlikely with bacterial pneumonia at this age. Although cold agglutinins are frequently sent for the diagnosis of Mycoplasma infection, they are neither sensitive nor specific. Therefore, cold agglutinins are of no value and should not be ordered. Nasopharyngeal aspirate for viral antigens would be an appropriate test for detecting respiratory viruses. Although viral infections may cause many of the same symptoms as described in the vignette, the chills, the high fever, and the radiographic findings of bilateral patchy infiltrates are consistent with Mycoplasma infection at this age.

3. A 6-year-old boy presents to the emergency department in February with a 6-day history of febrile illness that was initially characterized by the abrupt onset of elevated temperature (38.9), cough, coryza, sore throat, headaches, and malaise. The boy was evaluated by his pediatrician for those symptoms 5 days ago and tested positive on a rapid influenza diagnostic test. He seemed to be improving until 24 hours ago, when he had an increase in temperature to 39.9 and complained of shortness of breath. The boy has not received influenza immunization in the past year. A review of his symptoms reveals that he has had 3 episodes of boils on his buttocks that ruptured spontaneously over the past 6 months. On physical examination, he is sleepy and coughing with perioral cyanosis. The boy's temperature is 39.7, his respiratory rate is 36 breaths/min with intercostals retractions and grunting, and his oxygen saturation is 89% on room air.

Physical examination of his head, eyes, ears, nose, and throat does not show any abnormalities. Respiratory auscultation reveals diffuse crackles bilaterally with decreased breath sounds, and cardiac auscultation reveals no murmur, rub, or gallop. There are no lesions on the boy's extremities and his abdomen is benign and without organomegaly. Neurologically, he is sleepy but arousable and the remainder of the results from this examination are within normal limits.

Chest radiography shows diffuse interstitial infiltrates with right pleural effusion. The following are the results of the boy's laboratory tests: WBC 28.4 (75% N, 10% B, 10% L, 5% M); H/H 11.2/32.3; platelet count 353.

Of the following, the MOST likely pathogen responsible for this boy's acute deterioration is
A. group A B-hemolytic Streptoccocus
B. Haemophilus influenza
C. Mycoplasma pneumonia
D. Staphylococcus aureus
E. Streptococcus pneumoniae

Lower respiratory tract infection is the second most common complication of influenza after otitis media. The development of increasing respiratory distress 5 days into the course of influenza with marked toxicity and the increased white blood cell count with left shift in the boy in the vignette suggests secondary bacterial pneumonia. Staphylococcus aureus (including community-acquired methicillin-resistant S aureus), Streptococcus pneumonia, and group A Streptococcus are the leading organisms to consider in this setting. Bacterial coninfection with influenza, especially with S aureus, increases the risk of fatality. The recent history of recurrent boils reported in the child in this vignette suggests potential methicillin-resistant S aureus (MRSA colonization).

Group A Streptoccus is also associated with severe interstitial pneumonia that complicates influenza but is less common than S aureus. S pneumonia can complicate influenza infections as well but typically produces more focal consolidation in the lungs. Haemophilus influenza and Mycoplasma pneumonia do not typically cause illness as severe as described in this case and are not reported as common complications of influenza infection.

Other complications of influenza infection include neurologic syndromes that range from febrile seizures to encephalitis with status epilepticus or severe encephalopathy. Reye syndrome has been reported aspirin use during an influenza infection. Severe myositis (more common with influenza B infection) may occur. Myocarditis, pericarditis, and toxic shock syndrome (in association with S aureus or group A Streptococcus) are other rare complications of influenza infection.

4. A 17-year-old boy is applying for entry into military service and a complete history and physical examination. During the interview, he states that he is healthy, although he admits to being treated for three cases of pneumonia over the past 10 years. A chest radiograph performed during the last infection showed a left lower lobe pneumonia, and the patient states that the infection is "always on that side." The only finding of note on the physical examination today is slightly diminished breath sounds over the left lower lobe.

Of the following, the MOST likely cause for this boy's recurrent pneumonias is
A. bronchogenic cyst
B. congenital cystic adenomatoid malformation
C. congenital lobar emphysema
D. extrapulmonary sequestration
E. intrapulmonary sequestration

The presentation of recurrent unilateral pneumonias should prompt the clinician to consider congenital malformations of the lung, specifically pulmonary sequestration. Pulmonary sequestrations can be classified as intrapulmonary or extrapulmonary. Intrapulmonary sequestrations account for 75% to 90% of all sequestrations. Patients usually present in adolescence or adulthood with cough, wheezing, fever, and recurrent pulmonary infections. Surgical lobectomy generally is curative. Although also located on the left side in most cases, extrapulmonary sequestrations usually present prior to 6 months of age and often occur in conjunction with other congenital anomalies such as colonic duplication, pulmonary hypoplasia, or vertebral anomalies. Extrapulmonary sequestration can present similarly to intrapulmonary sequestrations, with cough, dyspnea, and infection, but also can result in feeding difficulty and, in rare cases, congestive heart failure due to increased shunting.

Bronchogenic cysts are the most common cause of a cyst in the lung. Most commonly located near central airway structures, bronchogenic cysts may present with symptoms of airway compression or infection, but they frequently are asymptomatic and discovered incidentally on chest radiography.

Congenital cystic adenomatoid malformation (CCAM) is another common congenital lung anomaly that typically is identified on prenatal ultrasonography. Most CCAMs present in the newborn period with respiratory distress and, depending on the type, may involve an entire lung, be associated with congenital anomalies, or result in fetal hydrops and pulmonary hypoplasia. Affected patients can present during childhood with recurrent pneumonia, but CCAM is less common than intrapulmonary sequestration at the age of the boy in the vignette.

Congenital lobar emphysema (CLE) is the most common neonatal cause of cystic malformation of the lung, and similar to CCAM, typically presents in the neonatal period with respiratory distress and airway obstruction.