Pneumonia

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Abstract

Respiratory diagnoses continue to make up a large number of admissions to the pediatric intensive care unit (PICU), most notably lower respiratory infections including pneumonia. This chapter will focus on pediatric community-acquired pneumonia (CAP), immunocompromised pneumonia, and aspiration pneumonia.

The pathogenesis for developing pneumonia varies; it can occur by direct inhalation of infectious particles in the air or aspiration, direct extension from the upper airways, and hematogenous spread. There are multiple levels of defense against pathogen invasion including anatomic barriers, as well as innate and adaptive immunity, which may be compromised in PICU patients.

The etiologies of pediatric pneumonia vary depending on age, host condition, and environmental factors like time of year and location. Viruses remain the most common form of lower respiratory tract infection in children, especially in neonates. Community-acquired bacterial pneumonia continues to be most prevalent in younger children as well, most often affecting children less than 5 years of age who are otherwise healthy. Despite immunizations and public health initiatives, the most common bacterial causes of CAP have remained largely unchanged over the last several decades and include: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* (including non-typable strains) and *Moraxella catarrhalis*. Pulmonary infection in an immunocompromised host provides a much broader differential and must be aggressively treated without delay.

This chapter will also address various imaging modalities and typical findings with pediatric pneumonia. Methods for pathogen identification are broad and range from non-specific markers of illness to invasive techniques for culture. The mainstay of therapy continues to be antibiotics tailored to the patient and presumed etiology; more novel therapies may include corticosteroids or macrolide antibiotics for immune modulation. In those patients with pneumonia with effusion or empyema, drainage therapies with thoracostomy tubes or a VATS procedure may be indicated.

Keywords

Pediatric • Pneumonia • Critical care • Antibiotics • Effusion • Empyema

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Introduction

Respiratory diagnoses continue to make up a large number of admissions to the pediatric intensive care unit (PICU) [1]. Lower respiratory tract infections are considered to be any infection beneath the anatomic level of the vocal cords, including bronchitis, bronchiolitis, tracheitis, and pneumonia [2]. Pneumonia remains an important cause of pediatric morbidity and mortality. There are nearly two million pneumonia-related deaths worldwide each year among children 5 years of age and younger [3, 4]. In the U.S., pneumonia causes over three million outpatient visits and more than 150,000 hospitalizations each year [5, 6]. In the developed world, early recognition and availability of antimicrobial therapies and respiratory support have lessened the mortality of pneumonia, but its morbidities remain. While widespread use of the heptavalent pneumococcal conjugate vaccine in 2000 was associated with fewer pneumonia-associated complications in infants <1 year of age, complications remained unchanged or increased in school-age children and adolescents [5]. Thus, despite our best efforts at prevention through vaccination, morbidities continue to plague our patients and pneumonia remains a common cause of pediatric hospital admission.

This chapter will focus on pediatric community-acquired pneumonia (CAP), immunocompromised pneumonia, and aspiration pneumonia. Hospital acquired pneumonia is an important type of lower respiratory infection found in the PICU, but it is discussed extensively in the chapter on Hospital-acquired Infections elsewhere in this textbook. The definition of pneumonia is generally accepted to be a lower respiratory illness with fever, respiratory symptoms including tachypnea, and often, radiologic evidence of parenchymal infiltrates [7]. The World Health Organization (WHO) has defined pneumonia solely based on clinical findings due to the lack of radiologic studies in many parts of the world [8].

Definition of Pneumonia and Guidelines for Admission to the Pediatric Intensive Care Unit

Determining the type of pneumonia can help guide clinical management. Previously healthy children presenting with the signs and symptoms of a lower respiratory tract infection are generally considered to have CAP. Aspiration involves inhaling foreign material beyond the vocal cords, often causing aspiration pneumonitis (chemical pneumonitis) or pneumonia (an infectious process secondary to the aspiration) [9, 10]. Commonly aspirated materials in children include oropharyngeal secretions, gastric contents, water, hydrocarbon, lipid, and foreign bodies [11]. Guidelines for admission to the ICU are available for both young children and adults, and are summarized in Table 6.1 [12, 13].

Table 6.1 Guidelines for ICU admission for children >3 months of age and adults from the Infectious Diseases Society of America and the American Thoracic Society

1a. Children >3 months of age
Need for invasive ventilation
Need for noninvasive positive pressure ventilation
Impending respiratory failure
Persistent tachycardia, hypotension, or need for pharmacologic hemodynamic support
SpO_2<92 % on FiO_2 ≥0.5
Altered mental status, whether due to hypercarbia or hypoxemia
Severity of illness scores, taken in context of clinical findings
1b. Adults
Need for invasive ventilation
Need for noninvasive positive pressure ventilation
Septic shock necessitating vasopressor support
Minor criteria (3 or >):
Respiratory rate >30 breaths/min
PaO_2/FiO_2 ratio <250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN > 20 mg/dL)
Leukopenia (WBC < 14,000 cells/mm^3)
Hypothermia <36°
Hypotension requiring aggressive fluid resuscitation

Adapted from Refs. [12, 13]

Pathogenesis

Pneumonia can occur by direct inhalation of infectious particles in the air or aspiration, direct extension from the upper airways, and hematogenous spread. Anatomic and cellular protection serves as the first line of defense against potential pathogens. Airway mucus traps inhaled toxins and microbes and helps to transport them up and out of the respiratory tract via ciliary beating and cough, a mechanism referred to clinically as mucociliary clearance [14]. When the microbe burden or virulence of the organism surpasses the abilities of these simple mechanical protections, the innate immune response is activated. The innate immunity is responsible for immediate recognition and control of microbial invasion. In mammals, conserved receptors enable rapid recognition of pathogens to begin elimination of the infection as well as initiate the adaptive immune response. Activating the innate immune receptors in the airway epithelium leads to mobilization and activation of dendritic cells, T cells, and B cells that amplify antigen recognition, antibody production, and further cellular recruitment and inflammation [15]. The specifics of these interactions and signaling cascades are beyond the scope of this chapter, but are further discussed in other chapters within this text.

The lower respiratory tract remains generally clear of pathogens [2]. The mechanisms by which microbes are able

to overwhelm defensive measures and result in pneumonia vary and depend on host conditions. The most common mechanism of pathogen entry is via inhalation of infectious particles, particularly in the case of specific organisms that spread via respiratory droplets such as *Mycobacterium tuberculosis*. Many viruses that cause lower respiratory tract infections are also spread utilizing aerosolized modes of transmission, including respiratory syncytial virus (RSV), influenza, and rhinoviruses. Due to their smaller size compared with bacteria, viruses consolidate more efficiently on smaller particles [16, 17]. Hematogenous spread results in pneumonia when bacteria in the bloodstream directly deposit in lung tissue.

Pulmonary aspiration can occur as a result of swallowing dysfunction, gastroesophageal reflux, anatomic anomalies such as tracheoesophageal fistulas, or an inability to protect the airway from oropharyngeal secretions. In the PICU, many patients have neurologic diseases that coexist with one, if not several, of these aforementioned mechanisms. Furthermore, impaired consciousness, as may occur with head injury, intoxication, sedation, and tracheal intubation, can also impair the ability to protect the airway, diminish the cough reflex, and exploit the patency of the anatomical connection between the larynx and trachea [9, 10, 18]. Direct aspiration of a large inoculum of infectious organisms can result when there is impairment of the host's anatomic defense, usually the gag and cough reflex. This most commonly occurs in children with profound neurologic impairment or during tracheal intubation [19, 20].

Etiologies

Community-Acquired Pneumonia

Viruses still remain the most common cause of lower respiratory tract infection, especially in infants [21]. The occurrence of primary viral infections and co-infections with bacterial pneumonia are receiving more attention in recent years due to advances in detection methods to improve the reliability and sensitivity in diagnosis [22]. Viruses have been found in approximately 50 % of sampled patients with a range of 43–67 %, although this prevalence is difficult to compare across studies that utilize different identification techniques [22–28]. The most commonly noted infectious viruses were rhinovirus, human bocavirus, human metapneumovirus (hMPV), and respiratory syncytial virus (RSV). Human metapneumovirus causes significant respiratory infection, accounting for 5–8 % of viral pneumonia cases [29, 30]. Human bocavirus, first described in 2005, is detected in up to 10 % of children with respiratory infections [31]. However, co-infection with another virus occurs in more than half of human bocavirus infected children, making its role as a predominant respiratory pathogen unclear. One possible explanation for the high prevalence of viral co-infection with human bocavirus is that this virus is shed in respiratory tract secretions for a longer period of time than other viruses [32–34]. Other important respiratory tract pathogens include adenovirus, parainfluenza viruses, and influenza A or B, all of which vary in prevalence based on season and epidemic periods.

The most common complication of viral pneumonia is a secondary bacterial infection. Bacterial co-infection occurs in about 15–33 % of pediatric patients hospitalized with a lower respiratory tract infection [23]. The most often occurring combination was rhinovirus and *Streptococcus pneumoniae*, though it remains difficult to interpret the causal role of rhinovirus in lower respiratory tract infections [23, 25]. RSV remains an important cause of bronchiolitis in infants and can often progress to pneumonia. A recent study noted that 40 % of children admitted to the PICU with RSV bronchiolitis had bacterial co-infection [35].

Community-acquired bacterial pneumonia continues to be most prevalent in younger children as well, most often affecting children less than 5 years of age who are otherwise healthy. Despite immunizations and public health initiatives, the most common bacterial causes of CAP have remained largely unchanged over the last several decades and include: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* (including non-typable strains) and *Moraxella catarrhalis* [7, 8, 21, 23]. In developing countries, other bacterial and viral etiologies must be considered, including *Mycobacterium tuberculosis, H. influenzae* type b (in unvaccinated areas of the world), and the measles virus [8].

In infants under 3–4 weeks of life, the most common etiologic agents include Group B *Streptococcus, Listeria monocytogenes,* and Gram-negative enteric bacteria. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (formerly *Chlamydia pneumoniae*), once considered to occur primarily among adolescents and young adults, are increasing being recognized as a cause of CAP in younger children, including those less than 5 years of age [21].

Immunocompromised Pneumonia

There are many causes of immunodeficiency in pediatrics including congenital, acquired (HIV/AIDS), or iatrogenic (during chemotherapy or after solid organ or stem cell transplant). These states can result in deficiencies in humoral immunity, cellular immunity, and neutrophil availability or function, making the host susceptible to not only typical pneumonia etiologies, but many opportunistic agents. Thus, the approach to an immunocompromised patient must be altered to consider the type and severity of immunodeficiency, as well as the temporal pattern after chemotherapy or

transplant. Other considerations that are important in immunocompromised patients include neutropenia, where a low white blood cell count can hinder the patient's ability to exhibit CXR findings and the lack of inflammation can alter the clinical presentation, and environmental factors and exposures that can cause geographic and temporal clustering of pathogens [11].

The causes of pneumonia following solid organ and stem cell transplant may follow a predictable temporal relationship. In the early post-transplant period (<1 month), infections from nosocomial or iatrogenic sources are most common. In the middle post-transplant period (1–6 months), donor-associated and opportunistic infections, including reactivation of latent infections, predominate; specific causes include *Cytomegalovirus* (CMV), Epstein-Barr virus (EBV) or Human Herpes Virus 6 (HHV6). Late post-transplant period (>6 months) etiologies include community-acquired infections as well as infections associated with profound immunosuppression [36, 37]. In an effort to diminish the risk associated with post-transplant immunosuppression, immunosuppressive agents (e.g., calcineurin inhibitors, high-dose corticosteroids) are used sparingly when possible and most protocols include anti-viral (especially CMV), anti-fungal, and *Pneumocystis jiroveci* (PCP) prophylaxis [36]. Still, many common infections continue to pose a great risk. For example, viral infections (e.g., RSV, influenza, adenovirus) cause greater virulence following solid organ or stem cell transplantation immediately after transplant when cellular immunity is profoundly low. Later in the course of transplantation, fungi such as *Aspergillus* spp. and *Candida* spp. become more prevalent causes of pneumonia with long-term steroid therapy [11, 37]. Thus, when a pulmonary process is suspected, aggressive treatment with broad-spectrum antibiotics, antifungals, and antivirals must be employed. Immunocompromised patients with pulmonary infiltrates may rapidly progress to respiratory failure and, thus, often require ICU care. Infection must be aggressively treated without delay, but other conditions must also be sought including pulmonary hemorrhage, malignancy, idiopathic pneumonitis, or cardiac disease [11, 38].

Aspiration Pneumonia

The clinical presentation of aspiration pneumonitis or pneumonia can vary and like other pneumonia etiologies, aspiration can result in acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) manifested by severe pulmonary inflammation and alveolar-capillary permeability injury. It is estimated that approximately one-third of patients with aspiration pneumonitis develop ALI/ARDS [39]. Etiologies of aspiration pneumonia depend if the aspiration is community acquired or hospital acquired. Bacteriologic studies in aspiration patients have shown that community acquired aspiration pneumonias are generally the same bacterium as CAP, including *H. influenzae*, *S. pneumoniae*, *S. aureus*, and enterobacteriaceae species. In those patients who aspirated in a hospital setting, the most common organisms cultured were gram-negative enteric bacteria including *Pseudomonas aeruginosa*. These recent studies failed to grow any anaerobic organisms, refuting the prior studies that endorsed anaerobes as common etiologies [10].

Diagnostic Approach

Imaging

The role for imaging in pediatric pneumonia is to detect the presence of pneumonia, determine the location and extent, and identify complications such as effusion or empyema. Modalities include chest radiographs (CXR), ultrasound (US), and computed tomography (CT) [11]. The presence of an infiltrate on CXR, combined with clinical and other laboratory findings can aid in the diagnosis of pneumonia. However, these modalities are not sufficiently sensitive or specific to reliably differentiate between viral, bacterial, and atypical bacterial causes [40]. The main use for US is to identify and characterize a parapneumonic effusion or empyema and provide image guidance for chest tube placement. This modality is limited by availability of equipment and operators. Chest CT is helpful to further evaluate difficult cases, particularly immunocompromised children with ill-defined infiltrates on CXR, complex empyema or effusion, or recurrent or chronic pneumonia [11]. Imaging findings in pneumonia can be non-specific, but when combined with other factors such as patient age, immune status, and historical information, they may help to narrow the differential diagnosis.

In viral pneumonia, the most common findings are bilateral symmetrical parahilar and bronchial opacities with or without atelectasis and air trapping; pleural effusions are rare (Fig. 6.1). This is in contrast to bronchopneumonia, a form of bacterial pneumonia that begins as peribronchiolar inflammation and spreads to the lung parenchyma. Bacterial pneumonia is characterized by consolidation and filling of the alveolar air spaces with exudate, inflammation, and fibrin. Bronchopneumonia is typical of many bacteria including *S. pneumoniae*, *H. influenzae*, *S. aureus*, and Gram-negative enteric bacteria. The CXR often reveals fluffy lobar consolidation or diffuse bilateral opacities extending peripherally, with or without associated pleural effusion. In aspiration pneumonia, the CXR may reveal ground-glass or consolidative opacities predominantly involving the middle and lower (dependent) lobes [41]. Finally, atypical pneumonia etiologies include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and, less commonly, *Legionella* species. The CXR findings for these atypical causes are varied. Diffuse

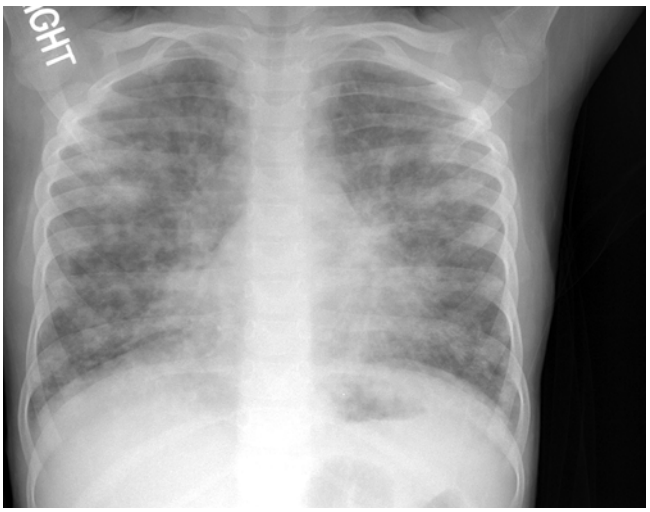

Fig. 6.1 Viral pneumonia. This CXR of a previously healthy 6 year-old child with varicella pneumonia shows diffuse alveolar infiltrates consistent with a viral pneumonia

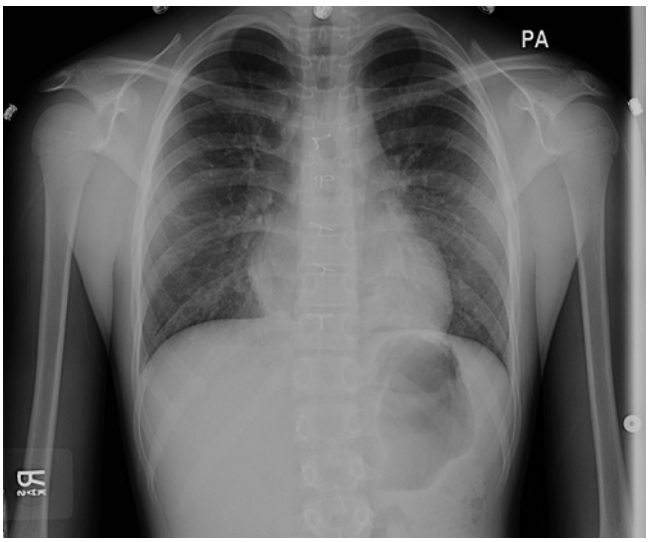

Fig. 6.2 Atypical pneumonia. This CXR of a 13 year-old boy with Mycoplasma pneumonia shows diffuse interstitial infiltrates (Reprinted from Swami and Shah [43]. With permission from McGraw-Hill)

interstitial infiltrates are characteristic though other findings include lobar consolidation, small bilateral pleural effusions, perihilar and peribronchial opacities that resemble butterfly wings, or a bi-lobar reticular pattern (Fig. 6.2) [42, 43].

The etiology of pneumonia in the immunocompromised patient can be difficult to determine though further imaging can help elucidate the cause. Respiratory failure in an immunocompromised child frequently necessitates a chest CT to better visualize the pattern and extent of disease, aid in diagnosis of the etiology, determine the need for more invasive procedures, and to increase the sensitivity of assessing treatment response [11]. Fungal infections are more difficult to diagnose; classic findings include pulmonary nodules on chest CT (Fig. 6.3).

Non-invasive Pathogen Identification

The "gold standard" diagnosis of pneumonia is microbiological identification of a pathogen from the lower respiratory tract [2]. Obtaining a LRT specimen can be difficult, especially in children, as it may require an invasive procedure and can be contaminated with oropharyngeal bacteria. Most children younger than 8 years of age cannot produce a sufficient sputum sample, defined as <10 squamous or epithelial cells and >25 polymorphonuclear white blood cells per low power field. Therefore, most samples are obtained through either an endotracheal tube via aspiration or bronchoalveolar lavage [44].

Other laboratory tests helpful in identifying the causative agent in CAP can include blood cultures, viral polymerase chain reaction (PCR) tests, and bacterial serologies. Commonly used diagnostic methods available for an individual microorganism may be found in Table 6.2 [8]. The clinician may also be limited by the capabilities of the laboratory in their institution for performing these tests.

Because of the difficulties in determining the etiology of pneumonia, non-microbiologic approaches have been sought to differentiate serious bacterial infections from nonbacterial pneumonia [21]. Many studies have evaluated markers including serum C-reactive protein (CRP), blood white cell count (WBC), serum procalcitonin (PCT), and erythrocyte sedimentation rate (ESR), attempting to find a test, or combination of tests, that would differentiate viral pneumonia from serious bacterial pneumonia necessitating antibiotic therapy [8, 45–49]. All of the aforementioned tests have limited utility in reliably differentiating viral from bacterial pneumonia, but when one or more of the markers are significantly elevated, a bacterial etiology is more likely. Thus, taken together with the clinical examination and radiologic findings, these tests can aid the clinician in deciding which patients require antibiotic therapy. PCT levels appear to be more sensitive than WBC, ESR, and CRP in identifying children with bacterial pneumonia and have been used to identify children who may benefit from a longer duration of antibiotic therapy [50].

Invasive Pathogen Identification

When non-invasive identification techniques are inadequate, or when identifying the cause is especially important, such as when treating an immunocompromised host, invasive diagnostic procedures may be necessary. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is the preferred diagnostic procedure in an immunocompromised host with an unknown

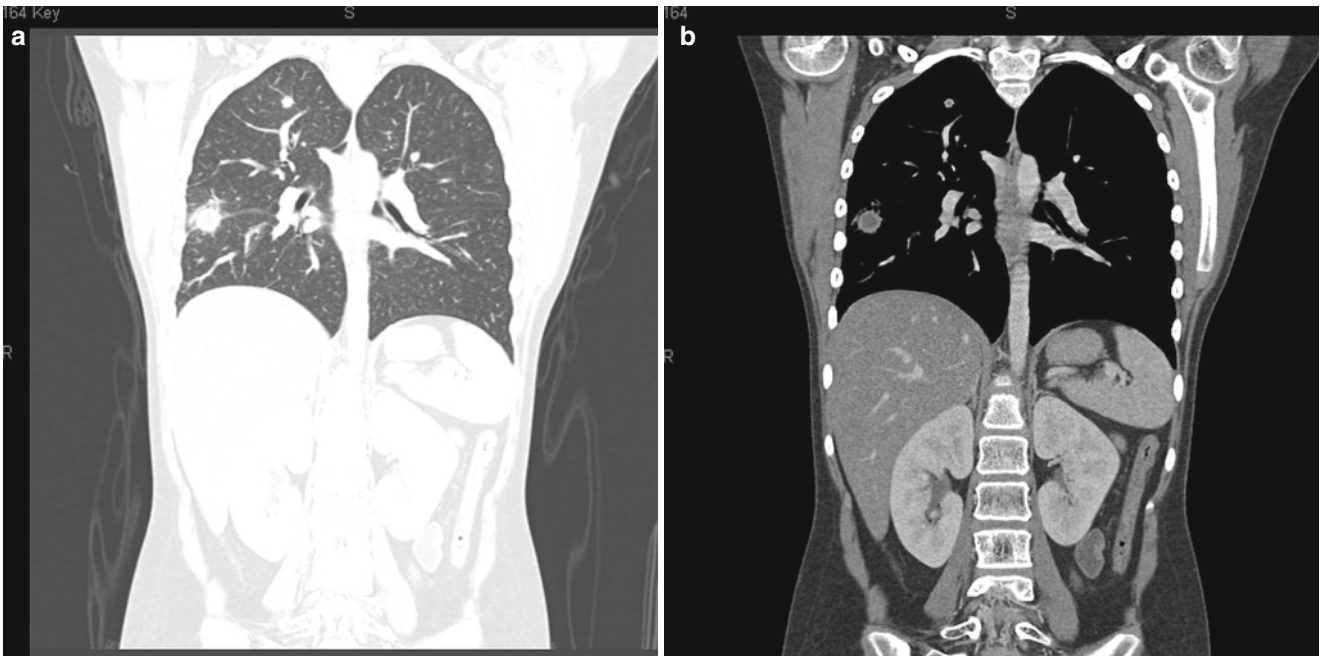

Fig. 6.3 Aspergillus pneumonia. Ten-year-old girl with AML and biopsy proven aspergillosis. (**a**, **b**) The chest CT (shown with two different window views) demonstrates a 0.6 cm nodule in the right upper lobe as well as a 1.5 cm × 1.5 cm centrally low attenuating mass lesion with peripheral enhancement noted in the posterior aspect of the right upper lobe, adjacent to the major fissure, consistent with an abscess

pathogen [51]. The sensitivity for diagnosis varies and depends on the host, pathogen, and the post-collection microbiologic detection methods employed. While many atypical organisms may be difficult to culture, *P. jiroveci* and *Mycobacterium* infections are more easily detected in BAL because of high organism burden in the lungs. The diagnosis of aspiration pneumonia is mainly clinical, often based on historical or witnessed events or conditions, and thus can be difficult to ascertain. If a BAL is performed in suspected aspiration, the presence of lipid-laden macrophages can help diagnose the aspiration of lipophilic foods such as formula [52]. A lipid-laden macrophage index can be obtained using the oil red O stain and when high, can be very sensitive and specific for aspiration [53].

Other invasive procedures include transbronchial biopsy if diffuse infiltrates are present but the BAL is negative, or CT-guided needle biopsy of a focal lesion. The improved diagnosis with these invasive procedures must be balanced against the risks to critically ill patients [54]. Important non-infectious etiologies to rule out with these invasive procedures include lung rejection (if transplanted), post-engraftment syndrome, idiopathic pneumonitis, graft versus host disease, and bronchiolitis obliterans.

General Treatment Principles

Antimicrobial Therapy

Children with severe pneumonia requiring admission to the PICU are likely to receive intravenous antimicrobial therapy even if only until the possibility of bacterial infection can be excluded. In critically ill children with respiratory failure from pneumonia, prompt initiation of broad-spectrum antimicrobials is crucial. One study in pediatric patients with CAP showed that longer delays in receipt of antibiotics were independently associated with adverse outcomes [55]. However, antibiotic resistance is increasing and the principles of appropriate antibiotic utilization must be adhered to: use of drug with narrowest spectrum, aiming for high tissue penetration, short half-life, and abiding to a short, intense duration of therapy [7]. The duration of therapy is typically 7–14 days, with 10 days being the best studied. A 7-day course may be reasonable in non-severe cases of pneumonia [12]. The choice of antimicrobial agent is based on many things including the patient's age, the type of pneumonia, and clinical and epidemiologic factors. Recent guidelines published by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America offer guidance for empiric antibiotic selection in children hospitalized with CAP (Table 6.3) [12].

Anti-inflammatory Therapy

Pneumonia causes a profound inflammatory response in the lungs and it has long been postulated that regulating this inflammation with steroid therapy may help to modulate local tissue damage and accelerate recovery for the patient. In addition, steroids are frequently utilized in other pulmonary inflammatory conditions such as reactive airway

Table 6.2 Microbiologic diagnosis of pneumonia in children

Microorganism	Preferred diagnostic method	Comments
Viruses		
Respiratory syncytial virus Influenza A or B Parainfluenza viruses Adenovirus Human metapneumovirus	Polymerase chain reaction (PCR) of nasopharyngeal secretions has the highest sensitivity; other options include immunofluorescence assay and solid-phase immunoassay	Viral culture has a high sensitivity but is less clinically useful as results may not be available for several days. In cases of adenoviral infection, serotyping may be helpful
Rhinovirus	PCR of nasopharyngeal secretions	The etiologic connection is not well established
Measles virus	Identify the virus by immunofluorescence assay or measure at least a quadrupling of serum antibody levels between acute phase and convalescence	The clinical diagnosis is specific
Varicella-zoster virus	Identify the virus by PCR or immunofluorescence assay of skin lesions,	The clinical diagnosis is specific. Diagnostic testing is useful to confirm the diagnosis. A four-fold increase in serum antibody levels between acute phase and convalescence is also diagnostic but clinically impractical
Hantavirus	Identify virus in nasopharyngeal secretions or antibody in serum. IgM or IgG antibodies may be found at presentation	Hantavirus infection is sufficiently uncommon that the finding of antibody in one serum sample is essentially diagnostic of acute infection
Cytomegalovirus (CMV) Epstein-Barr Virus (EBV)	Serologic studies: IgM and IgG for CMV; elevated IgM or IgG viral capsid antibody and absence of Epstein-Barr Nuclear Antigen (EBNA) confirms acute EBV infection	Finding virus in upper-airway secretions is not valuable with respect to diagnosis, since both CMV and EBV may be found in normal subjects. CMV antibody testing has poor specificity as past and recent infections cannot
Chlamydia		
Chlamydia trachomatis	Identify virus in nasopharyngeal secretions by culture or PCR assay	An IgM antibody test may be helpful
Chlamydophila pneumoniae	Identify virus in nasopharyngeal secretions by culture or PCR assay, or measure at least a quadrupling of serum antibody levels between the acute phase and convalescence	Etiologic connection in young children is not yet well established. The evidence is more convincing with respect to adolescents. No FDA tests exist for *C. pneumoniae* detection
Chlamydia psittaci	The finding of at least a quadrupling of serum antibody levels between the acute phase and convalescence	
Mycoplasma		
Mycoplasma pneumoniae	The finding of IgM antibody in serum late in the acute phase or early in convalescence is helpful, as is a positive PCR assay of secretions from a throat or a nasopharyngeal swab	Rapid IgM assays can provide results within 10 min. In younger children, an elevated IgM titer is often diagnostic; in older children, the finding of at least a quadrupling of serum antibody levels between the acute phase and convalescence is diagnostic. Cold agglutinin titers lack sensitivity and specificity and thus are no longer recommended
Bacteria		
Streptococcus pneumoniae *Haemophilus influenzae* *Streptococcus pyogenes* *Staphylococcus aureus* Gram-negative enteric bacteria Mouth anaerobes Group B streptococci *Neisseria meningitides*	Identify bacteria in culture of blood or pleural fluid; Pneumococcal urinary antigen tests accurately identify *S. pneumoniae* in pleural fluid	Culture of blood and pleural fluid lack sensitivity, especially in the setting of antibiotic treatment prior to culture. *S. pneumoniae* antigen tests may help confirm the diagnosis of S. pneumoniae when performed on pleural fluid; however, *S. pneumoniae* urine antigen test is not recommended because false-positives occur in the setting of pneumococcal colonization. PCR tests are accurate and increasingly available for *S. pneumoniae* and *S. aureus* detection in pleural fluid

(continued)

Table 6.2 (continued)

Microorganism	Preferred diagnostic method	Comments
Bordetella pertussis *Bordetella parapertussis*	Identify bacteria in culture, immunofluorescence assay, or PCR assay of nasopharyngeal secretions	PCR tests may be negative 3–4 weeks after illness onset. In such cases, serologic testing is recommended
Legionella pneumophilia and other legionella species	Identify bacteria in culture of sputum or tracheal aspirate or antigen in urine; or measure at least a quadrupling of serum antibody levels between the acute phase and convalescence	Culture of the organism requires special medium. Urinary antigen tests can detect only *L. pneumophila* antigen
Mycobacterium tuberculosis	Identify bacteria in acid fast culture of sputum or gastric aspirates, with or without a positive test for tuberculosis with purified protein derivative	Culture of bronchoalveolar lavage fluid is also specific but somewhat less sensitive. A PCR assay is more useful for the identification of the bacterium than for the detection of it. Interferon gamma release assays have modest sensitivity in children; a positive test can be diagnostic while a negative test does not exclude tuberculosis
Fungi		
Histoplasma capsulatum *Blastomyces dermatitidis* *Coccidioides immitis*	Identify organism by staining or culture of respiratory tract secretions; or measure IgM antibody or at least a quadrupling of serum antibody levels between the acute phase and convalescence	Histoplasma antigen is sometimes detectable in urine
Aspergillus spp.	Identification by culture or staining of respiratory washings; or serum EIA for Galactomannan antigen	Nested-PCR of serum may be useful if available. A single positive galactomannan test result should be clinically correlated by testing a separate serum specimen because some agents (e.g., piperacillin-tazobactam) may cross-react with the assay. If invasive aspergillosis is suspected in high-risk patients, serial sampling is recommended. The false positive rate is higher in children than adults [91, 92]

Adapted from McIntosh [6]. With permission from Massachusetts Medical Society

Table 6.3 Suggested initial drug therapies for pneumonia in children admitted to the PICU

	Community-acquired birth to 3 months	Community-acquired 4 months to 15 years	Immunocompromised	Aspiration
Typical pathogens	*S. pneumoniae*, *S. aureus*, Group B streptococci, Gram-negative enteric bacteria, *Listeria monocytogenes*, *Chlamydia trachomatis*, RSV, CMV	RSV, parainfluenza, influenza, rhinovirus, other respiratory viruses, *H. influenzae*, *S. pneumoniae, Mycoplasma pneumoniae*	In addition to typical pathogens: *Aspergillus*, *Candida*, herpes viruses, adenovirus, CMV, *P. jiroveci*	Typical aerobic flora and anaerobic flora including: *Peptostrepto-coccus, Fusobacterium* and *Bacteroides spp*
Recommended initial therapy	IV ampicillin and gentamicin in infants <20 days of age IV cefotaxime if >20 days of age	IV cefotaxime or IV ceftriaxone OR levofloxacin; addition of vancomycin or clindamycin for suspected MRSA; IV or PO azithromycin	In addition to antibiotics per age: amphotericin B or caspofungin, acyclovir for herpes, ganciclovir or foscarnet for CMV, trimethoprim-sulfamethoxazole or pentamidine for *P. jiroveci,* cidofovir for adenovirus	IV ampicillin-sulbactam or IV clindamycin; piperacillin-tazobactam if concern for gram negative enteric bacteria

Adapted from Refs. [8, 12]

disease (RAD) and acute respiratory distress syndrome (ARDS) [56]. The inflammatory responses in pneumonia and ARDS are similar with increases in pro-inflammatory cytokines concurrent with illness severity; severe pneumonia can often progress to acute lung injury (ALI) or ARDS [57–59]. While preclinical data support the use of steroids, current studies have not demonstrated a reduction in mortality among corticosteroid recipients compared with non-recipients. Several trials, however, have shown some secondary benefits of steroids, including reduced length of hospital stay and reduced inflammatory markers [60, 61]. In contrast, a multi-center, retrospective cohort study using administrative data found that among patients not receiving concomitant beta-agonist therapy (used as a proxy for wheezing), corticosteroid recipients had a longer LOS and higher readmission rate compared with non-recipients [62]. At present, the lack of high quality data supporting the efficacy of corticosteroids prevents the recommendation for the use of steroids in most patients with severe pneumonia. However, corticosteroids may provide benefit to certain subgroups of patients such as those with acute onset of wheezing and those who meet the criteria for ALI/ARDS [59].

Macrolide antibiotics have important anti-microbial as well as anti-inflammatory properties, though the relative importance of these two mechanisms in children with pneumonia is unknown. In adult studies, macrolides have recently been touted for their immunomodulatory effects and clinical benefit in multiple chronic pulmonary conditions such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). The specific immunomodulatory effects are vast and include inhibition of intracellular signaling to suppress the production of transcription factors such as NF-κB and decrease production of inflammatory cytokines that recruit neutrophils [63, 64]. Several recent studies in adult patients with severe CAP and sepsis have shown a benefit in survival in patients treated with macrolide antibiotics in addition to the recommended antibiotics based on pathogen [63, 65–68]. The role of macrolides in children with pneumonia is unclear. In pediatrics, several small retrospective studies have shown that among children with atypical CAP, those treated with macrolides were less likely to have persistence of signs and symptoms after 3 days of therapy [69, 70]. Among children with *M. pneumoniae* infection, Lu et al. found a shorter duration of fever among macrolide recipients compared with non-recipients [71]. Finally, a large multi-center study of 690 patients with *M. pneumoniae* infection defined by discharge diagnosis codes, the median length of hospital stay was 3 days (interquartile range, 2–6 days); macrolide recipients had a 32 % shorter length of stay compared with non-recipients [72].

Complications

Empyema and Effusion

Pneumonia-associated complications such as empyema affect 7.5–15 % of children hospitalized with pneumonia [5, 73–76]. The progression from simple parapneumonic effusion to empyema occurs in stages that represent a continuous spectrum (Table 6.4) [77]. In the first stage, there is a rapid influx of exudative fluid into the pleural space as a result of increased pulmonary interstitial fluid traversing the pleura and an increase in vascular permeability due to pro-inflammatory cytokines. The pleural fluid is marked by the absence of bacteria, fluid pH >7.20, normal glucose, and LDH <3 times the upper limit of normal. At this stage, drainage is not generally required for resolution but if the effusion becomes large and

Table 6.4 Characteristics of pleural effusions and empyema

Category	Fluid characteristics	Bacteriology	Drainage
1	Minimal, free-flowing (<10 mm rim of fluid or less than ¼ of hemithorax opacified)	unknown	Not typically required
2	Small to moderate, free-flowing (>10 mm rim of fluid or less than ½ of hemithorax opacified)	Negative gram stain and/or culture	Not typically required unless respiratory compromise
3	Large, free-flowing (opacifies more than ½ hemithorax); or loculated effusion; or effusion with thickened parietal pleura	Positive gram stain and/or culture	Yes
4	Empyema	Pus	Yes

Adapted from Refs. [12, 78, 93]

impairs respiratory mechanics, drainage might become necessary. The fluid in the pleural space can flow freely and often layers along the lateral chest wall in decubitus films or along the posterior chest wall in supine films [37, 78] (Fig. 6.4a, b). If left untreated, exudative effusions can progress to fibropurulent effusions characterized by the new presence of bacteria or positive microbial cultures. Cellular lysis and phagocytosis in the fluid can result in pH < 7.20, higher LDH, and low glucose. Loculations begin to develop, causing these effusions to now be referred to as "complicated." A chest radiograph may be difficult to interpret with respect to evidence of complicated effusions. Thoracic US is more accurate than chest radiographs in distinguishing simple from complicated pleural effusions. Complicated effusions are associated with floating debris and echogenic material or septations. Ultrasound is also useful in guiding pleural aspiration and drainage. Chest computed tomography (CT) may be indicated to better define pulmonary and pleural anatomy. Thickening of the parietal pleura on a contrasted CT scan is suggestive of empyema, even if the effusions are small in size (Fig. 6.4c). Finally, stage three is the organizing phase where fibroblasts grow into the pleural space and eventually results in a pleural peel, restricting chest mechanics. This stage often necessitates surgical decortication, especially if there is restrictive impairment [78].

The typical organisms responsible for the development of an empyema include *S. pneumoniae* and *S. aureus*. Pleural fluid cultures identify an organism in only 20–30 % of children with empyema. Blood cultures are positive in 13–30 % of children with empyema [79–82]. *S. aureus* is most often identified in pleural fluid culture. However, molecular identification techniques reveal that most culture-negative cases are attributable to *S. pneumoniae* [83, 84]. Regardless of the type of effusion present, antibiotic coverage based on treatment guidelines for pneumonia are essential. A recent study on the impact of early antibiotic therapy on the laboratory analysis of pleural fluid found that pre-treatment significantly hindered a bacterial diagnosis but did not alter the biochemical parameters of the fluid [85]. However, delaying antibiotic treatment for a thoracentesis would not be recommended in a critically ill child with respiratory failure secondary to pneumonia.

The treatment of complicated effusions and empyema remains controversial but recent studies have better defined protocols. A complete list of the available treatments for effusions and empyema is found in Table 6.5. Small, uncomplicated pleural effusions do not routinely require drainage. Moderate or large pleural effusions as well as those with evidence of septations or loculations usually require drainage. The medical options include appropriate antimicrobials and chest tube insertion with or without fibrinolytic therapy. Surgical options include video-assisted thoracoscopic surgery (VATS) or open thoracotomy and decortication. Recent guidelines concluded that chest tube drainage with the addition of fibrinolytic agents and VATS are equivalent methods of treatment and emphasize the importance of local expertise in determining the optimal approach for individual patients [12, 86]. VATS has gained popularity over conservative medical therapy as a way to directly visualize the pleural space, mechanically disrupt the adhesions, and strategically place the chest tube for optimal drainage [73, 87]. The higher cost and risk of anesthesia with VATS must be balanced against the more frequent requirement for additional drainage procedures for those undergoing primary chest tube placement. Thoracotomy and decortication are rarely needed.

The argument of medical management versus surgical management remains controversial. To date, at least two prospective trials in pediatrics have been completed directly comparing these methods. Both trials failed to show any outcome superiority with surgical management [80, 88]. Certainly children who have a very high white blood cell count in their pleural fluid (>15,000), poor output drainage by chest tube, low pleural pH, the presence of bacteria in the pleural fluid and/or bloodstream, or failure of medical therapy alone may benefit from early VATS [86]. Patients who underwent VATS required fewer

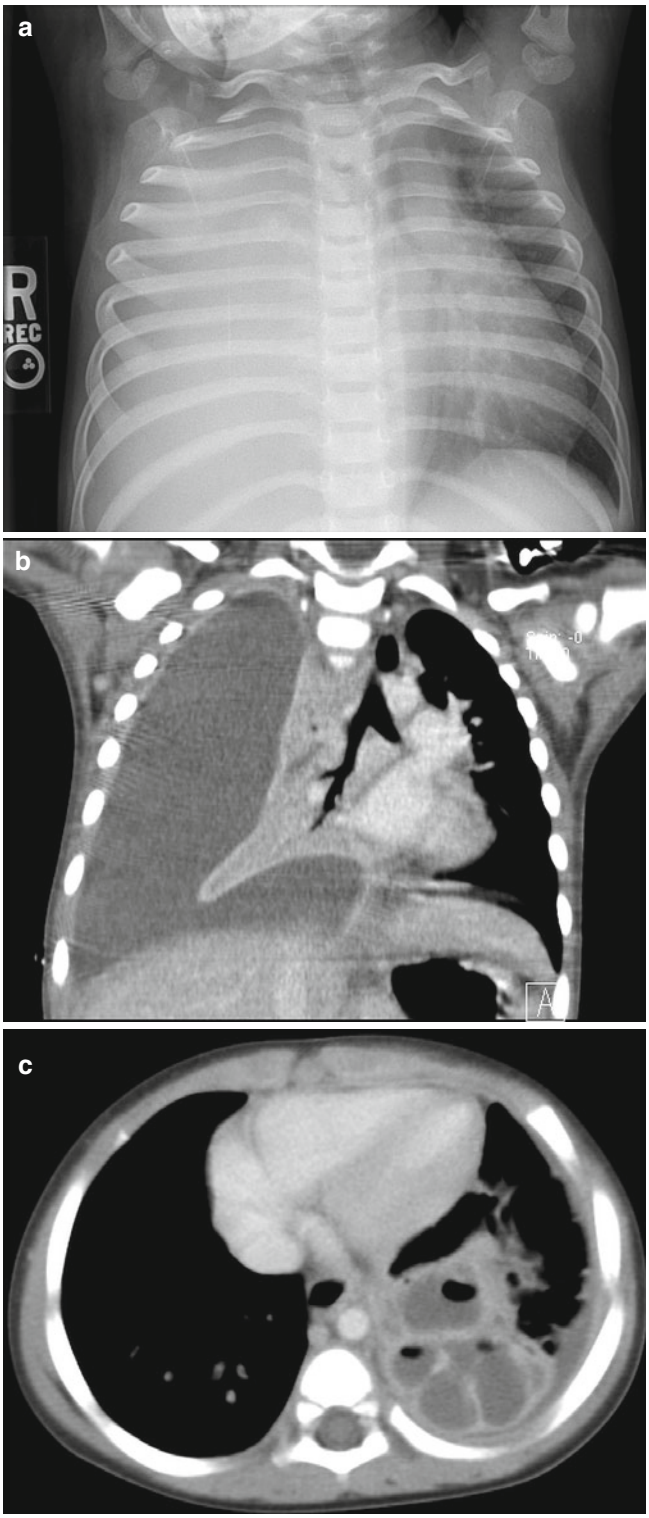

Fig. 6.4 Effusions and empyema. (**a**, **b**) A CXR shows complete opacification of the right hemithorax, with significant mediastinal shift to the left. The corresponding chest CT demonstrates a large right pleural effusion occupying the entire right hemithorax associated with leftward mediastinal shift. (**c**) A lobulated and loculated fluid collection with air-fluid levels is present in the left lower lobe measuring 4.5×4.4 cm with enhancing septations

additional drainage procedures, but had no difference in hospital length of stay [74]. However, one study of adults with empyema found that patients treated with a combination of tPA and recombinant human DNase required fewer surgical interventions and had a shorter length of hospital stay [89]. Cost-effectiveness, balance of risks, and availability of resources also plays a role in considerations for surgical management. A comparison of multiple strategies for pediatric empyema noted that the most cost effective method was insertion of a chest tube with fibrinolytic therapy [90].

Lung Abscess

Abscesses develop in localized areas of parenchymal infection that becomes necrotic and cavitates (Fig. 6.5a, b). Primary lung abscesses can develop either in previously healthy children or in children with underlying lung disease such as congenital cystic lesions, cystic fibrosis, or immunodeficiency. Mechanisms for abscess development can include direct aspiration of infectious material, embolic phenomena, hematogenous spread from septicemia, or local extension from abdominal or oropharyngeal processes. The most common organisms include Gram-positive bacteria such as streptococci, *Staphylococcus aureus* or anaerobes. Most abscesses resolve with intravenous antibiotics alone, but aspiration or drainage with a pigtail catheter may be necessary [37].

Prevention

Vaccines against specific bacteria that predominantly cause pneumonia in children, specifically pneumococcal conjugate vaccine (PCV-7) and *H. influenzae* vaccine (Hib) have drastically lowered the prevalence of infections causes by these strains. Since the introduction of PCV-7, several studies have documented its efficacy, and the decrease in cases of *H. influenzae* are equally striking [7, 21]. However, while PCV-7 has decreased the prevalence of invasive pneumococcal disease, the incidence of empyema is rising, the reason for which is unclear [76]. The licensure of pneumococcal conjugate vaccines that include even more serotypes (e.g., 13-valent) may further change the epidemiology of childhood pneumonia. Other vaccines, such as for measles (MMR) and influenza, can also aid to reduce these viral infections that so commonly lead to secondary bacterial pneumonia. While vaccines appear to be our greatest effort toward preventing pneumonia in children, more work needs to be done to increase their microbial coverage and availability throughout the world.

Table 6.5 Description of procedures for evacuating pleural effusion and empyema

Procedure	Description	Sedation requirement
Thoracentesis	Needle inserted between the ribs on the lateral chest wall into the pleural space, usually with ultrasound or computed tomography guidance	Local anesthesia, minimal (anxiolysis) or moderate sedation
Tube thoracostomy	Large bore, hollow, flexible tube placed between the ribs into pleural space though a 2 cm skin incision on the lateral chest wall. The tube is connected to a canister containing sterile water. Suction is applied to facilitate drainage	Local anesthesia, moderate or deep sedation
Video-assisted thoracoscopic surgery (VATS)	Operative technique in which a small camera and instruments are inserted into the pleural space through 2–3 small (1–2 cm) incisions of the skin and muscle on the lateral chest wall to mechanically remove purulent material and pleural adhesions. A thoracostomy tube is placed through one of the existing incisions following completion of the procedure	General anesthesia
Open thoracotomy	Operative technique where instruments are inserted into the pleural space through a single 5–8 cm incision of the skin and muscle on the postero-lateral chest wall to mechanically remove purulent material and pleural adhesions. A thoracostomy tube is placed through a second smaller 1–2 cm incision following completion of the procedure	General anesthesia

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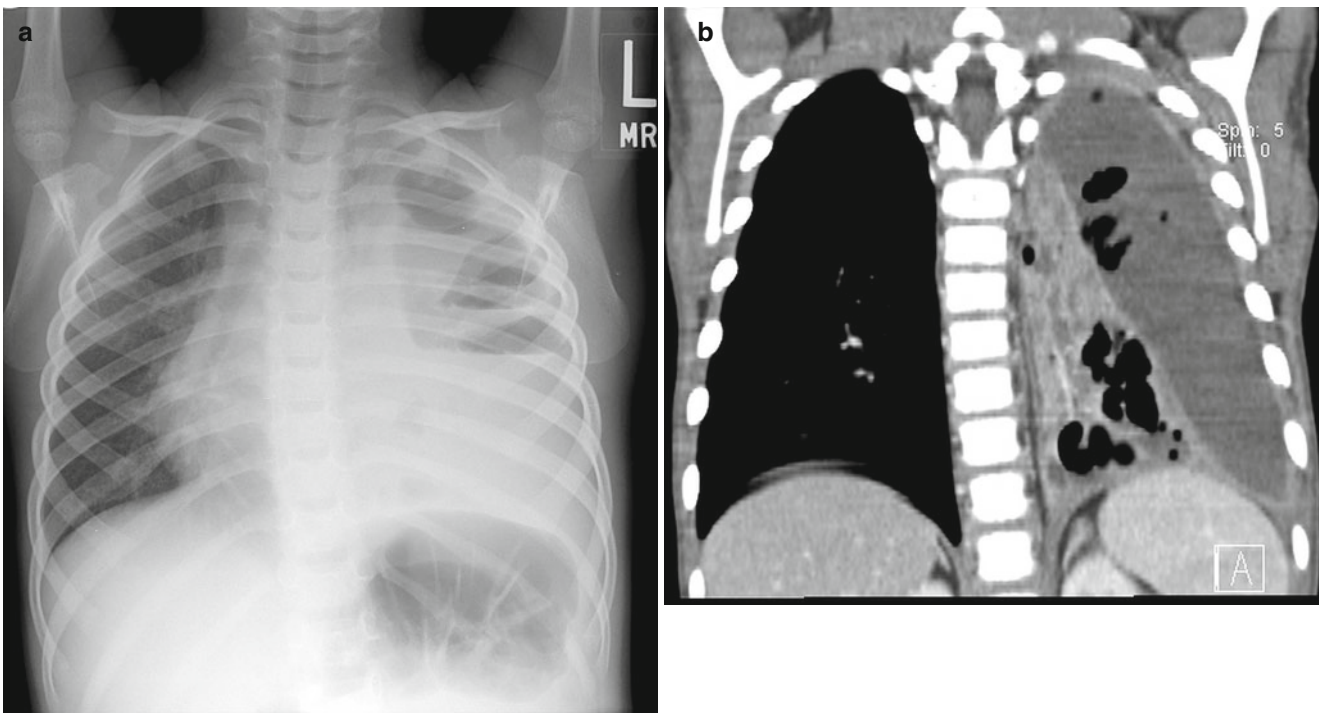

Fig. 6.5 Bronchial pneumonia with abscess. (**a**) The CXR shows a moderate left-sided effusion with fluid filled cystic spaces concerning for necrotizing pneumonia resulting in the shift of mediastinal structures to the right. (**b**) The corresponding chest CT shows a large loculated hydropneumothorax. The left lower lobe contains non-enhancing areas, multiloculated cavities, and air/fluid levels consistent with pulmonary abscesses and necrotizing pneumonia

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