Complicated pneumonia: current concepts and state of the art

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Purpose of review
This review aims to provide clinicians engaged in the care of infants and children an update on the current understanding of the epidemiology, etiology, diagnostic evaluation, and clinical management of complicated pneumonia. The review provides timely information surrounding areas of consensus and ongoing research.

Recent findings
The epidemiology and etiologies of complicated pneumonia continue to evolve over the past several decades in context of the introduction of new vaccines. We review uncommon and emerging pathogens. Immunocompromised patients are particularly at risk for complications. The 2011 clinical practice guidelines for pediatric community-acquired pneumonia from The Pediatric Infectious Diseases Society/Infectious Diseases Society of America and the British Thoracic Society are changing approaches to evaluation and management. The efficacy of new diagnostic laboratory studies, and imaging techniques, continues to be studied. Antibiotics are the mainstay of treatment, with several new options to consider. Techniques for the drainage of parapneumonic effusions continue to optimize.

Summary
Although much is known about complicated pneumonia, it remains a significant burden. New diagnostic and therapeutic interventions hold much promise. This review seeks to provide clinicians with evidence that motivates a reasoned approach to the evaluation and management of complicated pneumonia.

Keywords
community-acquired pneumonia, complicated pneumonia, parapneumonic effusion, *Streptococcus pneumoniae*

INTRODUCTION

Complicated pneumonia is a broad term that is commonly defined as an infection involving the lung parenchyma, which is complicated by one or more of the following: parapneumonic effusion, empyema, necrotizing pneumonia, abscess, pneumothorax, and bronchopleural fistula [1]. Although most community-acquired pneumonia (CAP) is uncomplicated, it is important to consider evaluation for complicated pneumonia in otherwise healthy children who are not responding to therapy, or in children with underlying comorbidities, such as an innate or acquired immunodeficiency, chronic lung disease, or underlying congenital pulmonary anatomic malformations. In this review, we describe the epidemiology, etiology, diagnosis, and treatment of complicated pneumonia.

EPIDEMIOLOGY

Pneumonia is the leading cause of mortality in the world in children less than 5 years of age. The incidence varies greatly between developed and developing countries with a far higher burden in the latter [2]. Pneumonia is the principle diagnosis leading to hospitalization in the less than 17-year-old age group in the United States [3]. The introduction of vaccinations against *Haemophilus influenzae* type B (HiB) and *Streptococcus pneumonia*e had a significant impact on the incidence of pneumonia and related hospitalizations. HiB as a cause of

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KEY POINTS

- *Streptococcus pneumoniae* remains a major bacterial pathogen despite substantial advances in vaccine development and widespread implementation.
- Microbiologic diagnosis of complicated pneumonia remains a challenge, particularly for bacterial pathogens.
- Treatment remains focused on antibacterial therapy, with new drugs antibiotics emerging.
- There are multiple options for drainage for parapneumonic effusions, with ongoing research to determine optimal approaches.

pneumonia has essentially been eradicated after the introduction of the vaccine in the United States.

The prevalence of all complications of CAP is not known. The rates of empyema vary widely across countries. As outlined in Fig. 1, a recent study revealed that the annualized hospitalization rates for empyema in children in the United States is around 2 per 100 000 population and has changed over the span of the introduction of the pneumococcal conjugate vaccines (PCVs). Overall, the rates were similar in the pre-PCV7 and post-PCV13 period, but were significantly lower post-PCV13 for children less than 2 years of age [4]. The rate in New Zealand, however, has increased from 1 per 100 000 in 1998 to 10 per 100 000 in 2012 with *Staphylococcus aureus* as the most commonly identified pathogen [5]. Huang *et al.* performed a prospective study to determine risk factors for progressive disease in children hospitalized for CAP. They found age less than 2 years, presence of pleural effusion at admission, low hemoglobin, elevated white blood cell count, and increased days to defervescence as key predictors for pneumonias that may fail to respond to therapy. *S. pneumoniae* was the etiological agent identified in about 58% of those that developed complications [6].

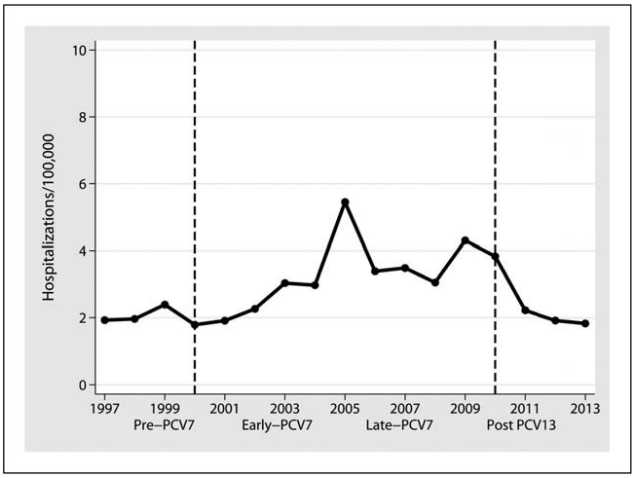

FIGURE 1. Annualized rates of empyema-related hospitalizations were similar in the post-PCV13 and pre-PCV7 time periods. Empyema hospitalizations per 100 000 children less than 18 years of age in the United States. Reproduced with permission from [4].

ETIOLOGY

Accurate data on etiology of pneumonia in children is lacking for several reasons. A recent article by Feikin *et al.* elucidates these challenges. As the authors note, there is heterogeneity in case definition of pneumonia because it is more a syndrome of findings rather than presence of one clinical finding. Making a microbiological diagnosis is often challenging in that noninvasive respiratory sampling lacks sensitivity and invasive procedures to reach the lower respiratory tract are often not undertaken. In cases where an invasive procedure is performed, the ability to procure a pathogen through testing may also be reduced due to pretreatment with antibiotics. Further, there may be difficulty with interpretation of the microbiological results as being a true pathogen versus a colonizer [7].

There have been many different multicountry attempts to identify the etiology of pneumonia in developing countries. The GABRIEL study (Global Approach to Biological Research, Infectious Diseases, and Epidemics in Low-income countries) was conducted in eight developing countries and found that *S. pneumoniae*, respiratory syncytial virus (RSV), human metapneumovirus (hMNV), parainfluenza and influenza were the most common microorganisms associated with pneumonia [8]. The PERCH study (Pneumonia Etiology Research for Child Health) is using the latest polymerase chain reaction (PCR) testing and standardized methodologies to identify etiology of pneumonia in seven developing countries [9]. The Centers for Disease Control and Prevention Etiology of Pneumonia in the Community (EPIC) study looked at the microbiological diagnosis of CAP that led to hospitalization in three hospitals in the United States. The study found that the burden of hospitalization was noted to be highest among children younger than 5 years of age, and viruses were identified as the most common etiology [10]. Identification of coinfections is increasingly common. Serious outcomes and complications, such as parapneumonic effusions, need for mechanical ventilation, intensive care unit admission, and longer length of stay, were found to be significantly higher in patients with bacterial pathogens alone and in those with

coinfections with viruses [11▪]. Bacterial coinfection in cases of influenza virus infection is a known cause for complications, including death. Post-mortem lung examination of 77 fatal cases of 2009 H1N1 influenza identified bacterial pathogens in 22 of the cases and included *S. pneumoniae, Streptococcus pyogenes,* and *S. aureus* [12].

S. pneumoniae is one of the most common bacterial causes of CAP. The introduction of PCV has resulted in significant decline of invasive pneumococcal disease (IPD). The seven-valent PCV7 was introduced in the United States in 2000 leading to substantial decline in rates of IPD caused by PCV7 serotypes. Subsequent years, however, noted a rise in non-PCV7 serotypes causing IPD. In 2010, 13-valent vaccine PCV13 replaced PCV7. Moore *et al.* report a substantial and rapid decline in IPD in children and adults within 3 years of introduction of PCV13 [13]. Although there was decrease in IPD, a cross-sectional, retrospective, cohort study that looked at hospitalized CAP pre-PCV7 and post-PCV7 between 1997 and 2006 noted an increase in local complications, which predominantly was empyema, in all age groups [14]. This increase in local complications could be due to nonpneumococcal bacterial pathogens such as *S. aureus*, as CAP hospitalization due to pneumococcal pneumonia was found to have significantly decreased after introduction of PCV13 [15▪▪]. Luca *et al.* assessed the population-level impact of PCV on pneumonia hospitalizations and related costs in Ontario, Canada and found that pneumococcal vaccination substantially reduced pneumonia-related hospitalizations and related costs among young children as well as in older children and adults. The benefits of vaccination extended beyond the vaccine recipients and a sustained reduction in pneumonia hospitalization rates 15 years after the licensure of PCV7 with further reduction after introduction of PCV13 was noted in this study [16]. Similar decline in hospitalization rates in young children after introduction of PCV was reported in Netherlands [17].

S. aureus including methicillin-resistant *S. aureus* (MRSA) is an important cause of both community-acquired as well as hospital-acquired complicated pneumonias. The presence of the pore-forming toxin Panton–Valentine leukocidin has been associated with the ability of *S. aureus* to cause severe presentations of pneumonia [18].

Atypical bacteria such as *Mycoplasma pneumoniae* and *Chlamydia pneumonia* can be important causes of lower respiratory tract infection in children. Pneumonia due to mycoplasma can fail to respond to standard macrolide therapy and progress to complicated pleural effusions and necrotizing pneumonia [19]. Other less common causes of complicated pneumonia are detailed in Table 1 [20].

Immunocompromised patients are particularly vulnerable to pathogens that immune competent persons may harbor as colonizers. Bacteria such as *Nocardia* spp. can cause pulmonary nocardiosis with abscesses and cavitation. Patients with primary immune deficiencies, such as chronic granulomatous disease and solid organ or hematopoietic stem cell transplant recipients, are at higher risk for *Nocardia* infection. Nontuberculous mycobacteria can cause complicated pneumonia in patients with underlying pulmonary disease like cystic fibrosis and in immunocompromised patients. Although *Mycobacterium avium* complex is an AIDS defining illness, the clinical manifestation is most often lymphadenitis or disseminated disease [21]. Environmental molds, such as *Aspergillus* spp. and *Mucorales* spp., can cause complicated pneumonia and disseminated disease in children with underlying hematological malignancies, conditions requiring prolonged immunosuppressive medications, and diabetes mellitus. *Cryptococcus neoformans* is a yeast that is found in soil contaminated with pigeon and bird droppings, and can cause pneumonia in immunocompromised hosts, including uncontrolled HIV patients. *Pneumocystis jiroveci* is another fungus almost exclusively pathogenic to immunocompromised hosts.

Uncommon but emerging pneumonia causing pathogens with high mortality rates must be considered in patients that have travelled to endemic areas. There has been a marked increase in the number of human infections with avian influenza A (H7N9) in China raising concern for pandemic influenza. Human infection occurs as a result of contact with infected poultry but human to human transmission occurs. The case fatality following the infection is 35–40% [22].

DIAGNOSIS

The 2011 publications of clinical practice guidelines for pediatric community-acquired pneumonia from The Pediatric Infectious Diseases Society/Infectious Diseases Society of America (IDSA), and the British Thoracic Society were met with great enthusiasm by many in the pediatric community [1,23]. These guidelines serve as a roadmap for the diagnosis and management of CAP in otherwise healthy infants and children older than 3 months of age in both outpatient and inpatient settings and across a wide range of severity. Guidelines encourage identification of a microbiologic diagnosis to inform management of complicated pneumonias. There are a wide range of diagnostic choices which must be carefully considered and guided by the clinical context.

Table 1. Less common causes of complicated pneumonia.

Cause	Clinical entity	Exposure/risk factors	Additional information	Diagnostic studies
Hantavirus	Hantavirus pulmonary syndrome	Contact with infected rodents	Increased human disease follows increased rodent population	- Serology testing
Mycobacterium tuberculosis complex	TB	Close contact with person with active TB and travel to countries with high prevalence of TB. *Mycobacterium bovis* can be acquired by consumption of unpasteurized and contaminated dairy products	*M. bovis* pulmonary TB is clinically identical to that caused by *M. tuberculosis* As mode of acquisition can be by ingestion, it can also present as abdominal TB	- AFB smear, culture & NAAT on sputum or gastric aspirates, BAL, pleural fluid, lung biopsy, pleural biopsy or lymph node tissue
Gram negative bacteria (*Klebsiella* spp., *Enterobacter* spp., *Escherichia coli*, *Pseudomonas aeruginosa*)	Ventilator associated pneumonia or nosocomial pneumonia	Mechanical ventilation, immunocompromised status		- Bacterial culture on BAL - ETT aspirates are not reliable - may indicate colonization
Bacillus anthracis	Inhalational anthrax	Contact with infected animals or contaminated animal products, including carcasses, hides, hair, wool, meat, and bone meal	Clinical manifestation characterized by hemorrhagic mediastinitis, hemorrhagic pneumonia and pleural effusion	- Gram stain, culture and PCR testing on blood, pleural fluid and tissue samples
Francisella tularensis	Respiratory tularemia	Inhalation of contaminated aerosols during lawn mowing, brush cutting, or baling contaminated hay	*F. tularensis* can infect many different animal species	- Serology testing - Culture and PCR on blood, BAL, tissue samples
Yersinia pestis	Pneumonic plague	Bite of infected rodent fleas, contact with infected rodents or inhalation of respiratory tract droplets from a human or animal	Plague is a zoonotic disease of rodents and fleas and humans are incidental hosts	- Serology testing - Culture from blood, sputum or BAL
Chlamydophila psittaci	Psittacosis	Inhalation of aerosolized excrement or secretions from infected birds	Nearly all domesticated and wild birds can transmit *C. psittaci*	- Serology testing - Culture and PCR of respiratory secretions
Legionella pneumophila	Legionnaires' disease	Inhalation of aerosolized water contaminated with *L. pneumophila*	In children, legionnaires' disease typically affects immunocompromised hosts	- Urine antigen - Culture and DNA PCR of BAL, pleural fluid, lung tissue
Coccidiodes immitis and *Coccidioides posadasii*	Coccidiodomycosis	Travel/residing in endemic areas including southwestern United States, northern Mexico, and some parts of Central and South America	More severe disease occurs in persons with T-cell lymphocytic dysfunction, in persons of African and Filipino ancestry and infants < 1yo	- Serum immunodiffusion and complement fixation - Antigen in urine, plasma, serum and BAL - Sputum, BAL, tissue fungus culture
Histoplasma capsulatum	Histoplasmosis	Travel/residing in endemic areas and particularly engaging in activities like spelunking, construction, farming, and cleaning of buildings contaminated with bat/bird droppings)	*H. capsulatum* is found in most parts of the world. It is highly endemic in the central United States, particularly the Mississippi, Ohio, and Missouri River valleys	- Serology testing - Serum and urine antigen -Sputum, BAL and tissue fungus culture
Blastomyces dermatitidis	Blastomycosis	Travel/residing in endemic areas which are areas surrounding the Ohio and Mississippi River valleys and the Great Lakes		- Serology testing - Urine antigen - Sputum, BAL and tissue fungus culture

Data from [20] Red Book 2015 Report of the Committee of Infectious Diseases. AFB, acid-fast bacilli; BAL, bronchoalveolar lavage; ETT, endotracheal tube; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; TB, tuberculosis.

Initial laboratory testing in cases of complicated CAP should include a complete blood count with differential, inflammatory markers, blood culture, viral respiratory testing, and consideration for evaluation of atypical bacteria.

Laboratory evaluation for acute-phase reactants—white blood cell count, procalcitonin, C-reactive protein, and erythrocyte sedimentation rate—appears most useful in following response to therapy, rather than elucidating the etiology. A clinical algorithm using procalcitonin values to determine duration of antibiotic therapy for lower respiratory infections in children led to shorter antibiotic courses [24].

Guidelines agree that for CAP that is moderate to severe (which includes complicated pneumonias), obtaining blood cultures is advised [1,23]. This recommendation is guided by the belief that identification of a bacterial pathogen directs choice of antimicrobial agent which may improve outcomes and informs understanding of causative pathogens which can direct future therapy and vaccine development [1]. Since the guideline, several studies have attempted to further define the prevalence of bacteremia in hospitalized children with pneumonia. A multicenter study of children with radiographically confirmed pneumonia who were hospitalized for CAP, found a prevalence of bacteremia of 7%. However, in the subgroup of patients who had a pleural drainage procedure, 21.2% of these children were bacteremic, compared with 5.7% of the children without pleural drainage [25]. A recent large cross-sectional study of children hospitalized for CAP found that only 2.5% of patients had a blood culture that revealed a pathogen. Looking more closely at the patients defined as severe or complicated pneumonia, the prevalence of bacteremia was 4.2%, compared with 2.2% in the remaining cohort [26▪]. Although the low prevalence of bacteremia is notable, the authors note that their study criteria excluded children with chronic illness and other medical comorbidities.

Testing for viral pathogens is a necessary part of evaluation for complicated pneumonias. Although the EPIC study showed viruses were detected by PCR assay of nasopharyngeal or oropharyngeal swabs in 73% of children with pneumonia, the question of whether these viruses were truly causative of lower respiratory tract infection—or rather upper respiratory infection, or prior infection—remained unanswered [10]. To address this question, the prevalence of respiratory viruses identified by PCR in children with CAP enrolled in the EPIC study was compared with asymptomatic controls. This work suggested that of the 13 viruses studied, there were important differences, with influenza, RSV, and hMNV most likely to be associated with CAP [27].

Diagnostic testing for atypical bacteria including *M. pneumoniae* is a consideration in the correct clinical context, as it can be the cause of complicated CAP [19]. Serologic testing remains the most common diagnostic choice, though PCR testing is increasingly being employed [28].

Next steps toward a microbiologic diagnosis of complicated CAP center on obtaining samples that reflect the lower respiratory tract, including: sputum samples, pleural fluid, bronchoalveolar lavage (BAL), and lung biopsy.

Sputum samples can be used to identify microbes from the lower respiratory tract. CAP IDSA guidelines recommend in hospitalized children who can produce sputum, gram stain, and culture should be sent [1]. The authors noted children, unlike adults, often do not produce sputum, thus limiting the utility of this option. However, another option remains—sputum induction. The PERCH study took on the questions of safety and utility of induced sputum for diagnosis of pneumonia in young children. Despite determining the safety of sputum induction and assuring adequate quality lower respiratory specimens, the study authors were not able to find an association between a positive-induced sputum specimen for a bacterial organism and a radiographic diagnosis of pneumonia [29–31].

CAP IDSA guidelines suggest analysis of pleural fluid properties, such as pH, glucose, protein, and lactate dehydrogenase (LDH), is not recommended in the pediatric population [1]. Yet a recent study of pleural fluid in pediatric complicated CAP found that elevated LDH and lower levels of glucose values may serve as predictors for children who require prolonged hospital courses [32]. All pleural fluid should be sent for cell count and differential, as well as gram stain and culture. In addition, molecular diagnostic testing of lung and pleural aspiration is shown to improve detection of bacterial pathogens when compared to cultures alone [33].

The use of flexible bronchoscopy with BAL in severe complicated pneumonia is recommended in the CAP IDSA guidelines for patients who remain without a microbiologic diagnosis on initial testing [1]. Recent publications highlight the role of BAL in immunocompromised children, with one retrospective review citing the identification of pathogens in 31% of immunocompromised patients, the majority of which led to changes in antimicrobial therapy [34].

Characterizing complicated pneumonias with imaging is an essential step in determining treatment course. Traditionally, a chest radiograph is the first step, with particular focus on evaluating for

parapneumonic effusion. That being said, lung ultrasound is increasingly well described as an alternative to chest radiograph, with potentially lower costs, and absence of radiation exposure [35–37]. Ultrasound is also increasingly supplanting chest computed tomography (CT) as the preferred imaging choice for guidelines and institutional algorithms for managing parapneumonic effusions [1,38]. One report studying the implementation of an institutional complicated pneumonia pathway, which recommended chest ultrasound over chest CT, found reduced costs and radiation exposure, without changes in the clinical course [39].

TREATMENT

Antimicrobials are a major component of the management of complicated pneumonia, either as the sole approach, or in combination with surgical intervention. When a pathogen is identified, targeted therapy should be instituted as outlined in the CAP IDSA guidelines [1]. However, in many cases, the etiology remains elusive and empiric therapy is continued and adjusted based on patient's clinical response.

Multidrug-resistant pneumococcus and penicillin resistance in pneumococcus declined significantly following the introduction of pneumococcal vaccines [40]. The prevalence of macrolide resistance varies among countries. In the United States, macrolide resistance in pneumococcus isolates is ~30% but is significantly higher in Southeast Asian countries [41]. For patients with complicated pneumonia such as empyema, a third-generation cephalosporin is the recommended empiric agent. Addition of vancomycin or clindamycin should be considered if there is concern for MRSA infection. Similarly, addition of a macrolide should be considered if there is suspicion for atypical bacterial infection. For less severe presentations of complicated pneumonia, penicillin may still be considered as the initial choice for empiric therapy [1]. Although penicillin prescribing increased and cephalosporin prescribing declined for hospitalized pneumonia in children following the publication of the CAP IDSA guidelines, it is unknown if this holds true for patients with parapneumonic effusions [42].

Ceftaroline is a newer broad spectrum cephalosporin approved for pediatric use in the treatment of complicated CAP. It has greater in-vitro activity against pneumococcus compared with ceftriaxone and has activity against MRSA. A multicenter randomized trial to assess safety, tolerability, and efficacy of ceftaroline to ceftriaxone and vancomycin in pediatric patients with complicated CAP found it to be well tolerated with similar cure rates [43]. Daptomycin is a cyclic lipopeptide with excellent gram-positive activity including against MRSA. However, it is inactivated by surfactant and thus would not be recommended for use in treatment of pneumonia. Other agents in the pipeline with activity against MRSA being evaluated for use in pneumonia and yet to be approved for use in children include dalbavancin, telavancin, and tedizolid [44].

The duration of total antibiotic treatment and optimal time for transition from parenteral to oral therapy for complicated pneumonia is not established. The duration varies depending on the complication. For example, for lung abscess, the duration is for up to 4–6 weeks or longer in cases of a large cavitation. Such prolonged courses may also be given in patients with more severe presentations of empyema. Typically, therapy for complicated pneumonia begins with intravenous antibiotics. The switch to oral antibiotics in empyema could be considered once patient is afebrile for 1–2 days and the chest tube is removed [45]. In a multicenter retrospective cohort study, the treatment failure rates for between outpatient parenteral antibiotic therapy (OPAT) and oral therapy did not differ [46▪▪]. Peripherally inserted intravenous catheters (PICCs) used for OPAT can be associated with significant complications making enteral therapy effective, safer, and less expensive option [47].

In addition to antibiotic therapy, the management of parapneumonic effusion and empyema is increasingly being managed with drainage procedures. Studies have suggested improved clinical outcomes with surgical interventions rather than antibiotics alone [48]. Treatment approaches vary by size and quality of effusion. In general, parapneumonic effusions are classified on a spectrum of severity, from simple to complicated, based on degree of loculation and quality of fluid. Empyema is generally defined as a loculated effusion with purulent fluid and bacteria present, representing more severe disease [49]. The CAP IDSA guideline and an American Pediatric Surgical Association review point to the characteristics of the effusion as important in management decisions surrounding drainage and fibrinolysis [1,49]. Other authors have noted that fluid characteristics on ultrasound may not predict response to intervention [38]. In one study, complex septations on ultrasound were in fact associated with better outcomes [50].

With respect to choices for drainage, chest tube placement with fibrinolytic therapy appears to be increasingly more common than video-assisted thoracoscopic surgery (VATS) in U.S. children's hospitals [51]. This is supported by work over the last decade that has shown no superiority of VATS to chest tube placement with fibrinolytics with respect to clinical outcomes [52–56]. A recent Cochrane

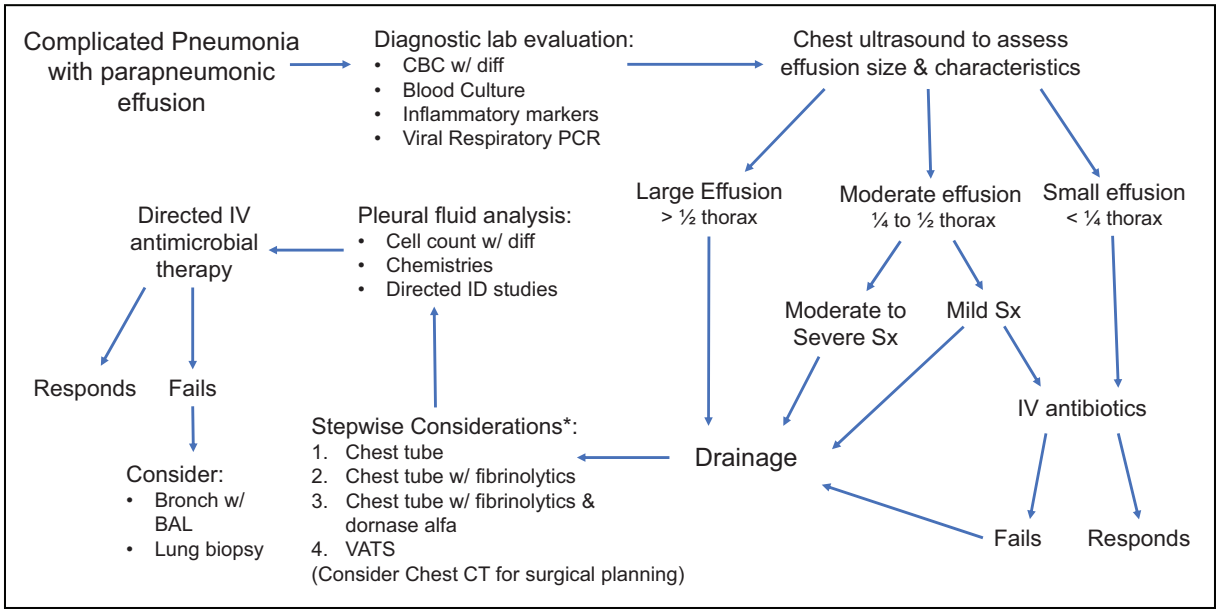

FIGURE 2. Pathway for evaluation and management of complicated pneumonia with parapneumonic effusion in children. On the basis of CAP IDSA guidelines, the authors created an algorithm for evaluation and management of complicated pneumonia with parapneumonic effusion. Data from [1]. *Stepwise considerations for drainage dependent on local provider expertise and institutional preference. BAL, bronchoalveolar lavage; Bronch, bronchoscopy; CT, computed tomography; IV, intravenous; US, ultrasound; VATS, video-assisted thoracoscopic surgery.

review noted no difference in mortality between management of empyema by VATS compared with chest tube placement in children and adults [57].

The choice of optimal fibrinolytic agent remains unknown. Based on encouraging results from an adult trial, there is an ongoing randomized controlled trial to assess the benefit of adding an intrapleural mucolytic agent (dornase alfa), in addition to a fibrinolytic (tissue plasminogen activator), compared with a fibrinolytic alone, for the treatment of pediatric empyema [58,59].

Using the CAP IDSA guidelines as a touchstone, Fig. 2 endeavors to outline an algorithm for the diagnosis and treatment of complicated pneumonia with parapneumonic effusion in children. Ultimately, as the guidelines note, the choice of drainage procedures, and further invasive testing for children not responding to therapy, is in large part dependent on local provider expertise and institutional preference.

CONCLUSION

Although much is known about complicated pneumonia in children, significant improvements are needed in the management of this heterogeneous disease. Using recent guidelines as a framework, emerging diagnostic testing strategies to determine the etiology and severity of pneumonia, and novel approaches to surgical and medical interventions, hold much promise for enhancing outcomes in this vulnerable population.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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