

ILLUSTRATIVE CASE

Something Doesn't Smell Right: When a Patient With Empyema Isn't Responding to Guideline-Based Management

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A 10-month-old girl presented with 5 days of fever and cough to our emergency department. She was diagnosed with an upper respiratory infection and discharged from the hospital without antibiotics. She returned 3 days later in severe respiratory distress. Her past medical history was significant for an admission at 3 months of age for community-acquired pneumonia. She had no other medical problems and was fully vaccinated for her age. Her parents denied any sick contacts, and there was no family history of immunodeficiency.

On presentation, her vital signs were notable for a respiratory rate of 56 breaths per minute, a heart rate of 187 beats per minute, temperature of 37°C, and a blood oxygen saturation of 93% on room air. She was grunting with both suprasternal and subcostal retractions. There were diminished breath sounds over the right lung field. Initial laboratories were remarkable for a white blood cell count of 67 000 leukocytes/ μ L and a C-reactive protein (CRP) >45 mg/dL. The patient had a chest radiograph that showed areas of consolidation in the right lung with a large right-sided pleural effusion involving over two-thirds of her right lung field and multiple air lucencies (Fig 1). A computed tomography scan of the chest with contrast showed a large, 2.6-cm, loculated pleural fluid collection with areas of peripheral rim enhancement in the right chest. There was extensive consolidation in the right middle lobe with the aforementioned small, ill-defined air lucencies concerning for cavitation and necrosis versus bronchopleural fistula (Fig 2).

Question *What are the current recommendations for management of a pneumonia complicated by an effusion?*

Discussion

The Infectious Disease Society of America (IDSA) pediatric pneumonia guidelines from 2011 detail the management of parapneumonic effusions based on the size of the effusion and the degree of respiratory compromise.¹ Moderate effusions involve more than one-fourth but less than one-half of the lung, and large effusions obscure more than one-half of the lung. Both the IDSA and the American Pediatric Surgery Association guidelines recommend drainage for moderate parapneumonic effusions associated with respiratory distress, large parapneumonic effusions, or documented purulent effusions.² For drainage, both chest-tube with fibrinolytics and video-assisted thoracoscopy

CASE

www.hospitalpediatrics.org

DOI:10.1542/hpeds.2015-0274

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HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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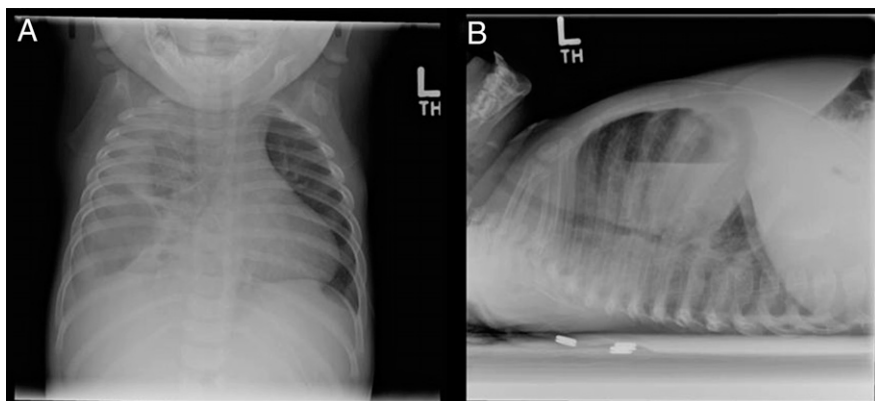


FIGURE 1 A, The posterior-anterior view of the chest radiograph demonstrating the large right-sided pleural effusion with consolidation in the right lung base. B, The cross-table lateral view of the chest radiograph demonstrating the air-fluid level present in the right lung cavity.

(VAT) have been shown to be effective. Multiple studies have now shown clinical equipoise between the 2 therapies but note higher costs associated with VAT.^{5,4} Therefore, VAT is not typically first line, but multicenter equivalence studies comparing clinical outcomes such as pain, long-term pulmonary function, and exercise tolerance have not yet been performed.^{5,6} Because the evidence is not clear, the IDSA guidelines currently suggest that choice of drainage modality be based on local expertise. In fact, there is some controversy that drainage is even necessary. In 2010, Carter et al reviewed their experience with 182 children and found that clinically stable patients with small or moderate-sized effusions could be managed with antibiotics

alone.⁷ Patients with large effusions, mediastinal shift, respiratory distress, or need for ICU-level care were still likely to undergo early pleural drainage. Ultimately, evidence suggests that outcomes are excellent and similar, regardless of treatment choice.⁸ In our patient, the significant size of the effusion and degree of respiratory distress led us to proceed with drainage.

Case Continuation

The patient underwent a VAT with right lung decortication. Fifty milliliters of purulent fluid was drained. The patient was transferred to the ICU on mechanical ventilation. Vancomycin and ceftriaxone were initiated for presumed community-acquired pneumonia complicated by empyema. The Gram stain of the pleural fluid revealed moderate white blood cells, moderate Gram-negative rods, and rare Gram-positive cocci. However, the pleural fluid culture initially remained negative. After 3 days of antibiotics, the patient continued to have high fevers, her inflammatory markers remained elevated, and she continued to require mechanical ventilation.

Questions *How should physicians gauge response to antimicrobial agents in complicated pneumonias? What common and unusual organisms are implicated in empyema?*

Discussion

The IDSA pneumonia guidelines define a nonresponder as a patient who shows a

lack of improvement within 48 to 72 hours after the initiation of therapy.¹ Factors to consider when gauging responsiveness include persistence of fever, worsening respiratory distress, changes clinically or on physical examination, inability to maintain oral hydration, increasing or unchanged CRP, and radiologic results. Further radiographic images or studies from the pleural fluid may help to identify a pathogen so antibiotic therapy may be tailored.

Initial empirical antimicrobial choices for complicated pneumonias are similar for uncomplicated pneumonias because both have the same causative organisms. Current guidelines endorse the empirical use of ampicillin for suspected *Streptococcus pneumoniae*, but this would not cover *Staphylococcus aureus*, the other common organism that should be considered in severe cases.¹ For patients who are improving, recent literature suggests that oral therapy is as effective as prolonged home parenteral antibiotics.^{9,10}

Since the introduction of the pneumococcal vaccine (PCV-7), there has been a decrease in hospital admissions for pediatric pneumonia. Conversely, studies have shown that pulmonary empyema hospitalization rates increased nationally by almost 70% from 1997 to 2006.^{11,12} A specific organism is identified in only ~30% of cases.¹² Grijalva et al found that rates of unspecified empyema increased 1.89-fold from 1996 to 2006, with a 3.09-fold increase in rates of unspecified empyema in patients aged 2 to 4 years.¹¹ Studies using molecular diagnostic techniques such as ribosomal polymerase chain reaction have found that the majority of culture-negative empyemas are caused by *S pneumoniae*.¹³⁻¹⁵ Yet an important fraction of empyemas have other etiologies. In 1990, Brooks reported 13 years of empyema culture results taken from 72 patients which identified 93 organisms.¹⁶ The most common were *Haemophilus influenzae*, *S pneumoniae*, and *S aureus*, but a multitude of other aerobic bacteria including *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* were identified. There were also high rates of anaerobic bacterial infection, especially *Bacteroides* spp, *Fusobacterium*

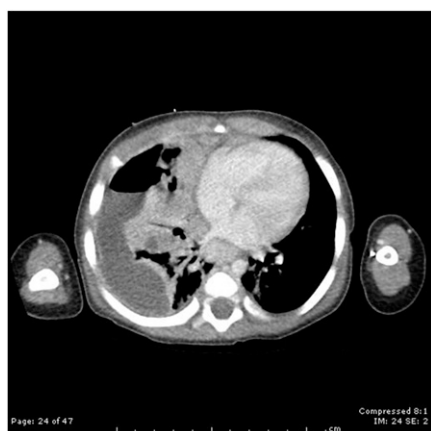


FIGURE 2 Computed tomography scan of the chest with contrast demonstrating the large right-sided pleural fluid collection, a visible air-fluid level, and peripheral rim enhancement.

spp, and *Peptostreptococcus* spp. These organisms are often fastidious and difficult to grow in culture.

CASE CONTINUATION

The primary team met with the pediatric surgeons and infectious disease specialists, and it was noted that the pleural fluid during the VAT was particularly foul smelling. Given this information and the polymicrobial results of the Gram stain, ceftriaxone was replaced with piperacillin-tazobactam to provide better anaerobic coverage. Over the next 24 hours, the patient became afebrile and was successfully extubated. On hospital day 6, *Campylobacter rectus* was identified in the anaerobic pleural fluid culture.

Question *How are C rectus infections usually acquired or transmitted? How common are anaerobic pediatric pulmonary infections?*

Discussion

Campylobacter rectus is a microaerophilic, curved Gram-negative rod that makes up part of the human oral flora. It is a well-described cause of periodontitis in both children and adults.^{17,18} However, invasive disease has only been reported in 7 adult case reports, which detailed conditions such as intracranial abscesses, spinal abscesses, and soft tissue infections.¹⁹⁻²³ Most individuals had poor oral hygiene and comorbidities that may have contributed to a weakened immune response. Given the low number of cases, there are limited data regarding the antimicrobial susceptibility pattern for *C rectus*. In several cases, the patients demonstrated clinical improvement after treatment with amoxicillin-clavulanate.^{19,23} Antimicrobial susceptibility testing was not performed on our patient's isolate of *C rectus*. Nonetheless, her clinical improvement coincided with the initiation of piperacillin-tazobactam.

Our patient differs from previous cases in that she was a previously healthy child with no active dental disease at the time of her illness. However, the patient's mother had poor dentition, and vertical transmission of maternal oral bacteria to an infant can occur.²⁴⁻²⁷ The American Association of Pediatrics Section on Pediatric Dentistry

targets improving maternal oral health to delay colonization in infants as long as possible.²⁸ Several studies have shown that bacteria implicated in periodontitis, including *C rectus*, can colonize the oral mucosa of young infants even before they develop primary dentition.²⁹⁻³¹ In an epidemiologic study that evaluated the age range of initial colonization of periodontal pathogens, Cortelli et al demonstrated that colonization of the oral cavity by *C rectus* occurs as early as 0 to 4 months of age and that the presence of teeth was not necessary for colonization.³² Therefore, despite the absence of teeth in our patient, her oral mucosa was likely already colonized with *C rectus*.

Traditionally, anaerobic pulmonary infections in pediatric patients have been considered rare. However, overall rates of anaerobic infections may be underreported given the difficulty in isolating and culturing the organisms in the past.^{16,33} Such infections generally affect children with poor oral hygiene or children who are at risk for aspiration of their oral secretions or gastric contents. One study identified anaerobic bacteria in 33% of 72 neurologically impaired pediatric patients with empyema.¹⁶ The most common lower respiratory tract infections where anaerobes are identified are aspiration pneumonia, lung abscesses, and empyema. Intriguingly, it has been suggested that foul-smelling pleural fluid may suggest the presence of anaerobic bacteria.³³ This underscores the importance of communicating important intraoperative findings between surgeons and the primary care team.

Case Continuation

Vancomycin was discontinued, and the patient was transitioned from piperacillin-tazobactam to ampicillin-sulbactam. The patient's leukocyte count and CRP trended down during her hospitalization. Before discharge, the patient underwent an immunodeficiency workup. She had normal T-cell subsets, natural killer cells, and B cells. Immunoglobulins were normal or elevated. An HIV screening test was negative. Her initial *Haemophilus influenzae* type B and pneumococcal vaccine antibody titers were just below the lower range of

normal for a previously vaccinated child. After 12 days of hospitalization, the patient was discharged from the hospital on oral amoxicillin-clavulanate to complete a 4-week course of antibiotics. The patient was scheduled to receive repeat vaccinations and have repeat titers drawn; however, she was lost to follow-up. We reviewed her laboratory findings with an immunologist who felt that the suspicion for an immunodeficiency was low.

Question *When should a child with an unusual bacterial infection undergo an immunodeficiency workup?*

Discussion

A child with infections that are too frequent, too severe, or too long-lasting should be considered for primary immunodeficiency (PI) evaluation. In our patient, her infection was categorized as "too severe"; the rarity of the organism further prompted a consideration of PI. However, she did not have other clinical features that typically raise suspicion for PI, such as failure to thrive, ≥ 2 pneumonias within 1 year, chronic diarrhea, nonhealing wounds, lymphopenia, unexplained fevers, or recurrent candidiasis.³⁴ Family history of immunodeficiency has also been shown to be the most predictive factor of any PI.³⁵ If PI is suspected, a thorough history and physical examination should be able to narrow further investigation to support abnormality in 1 of 4 immune system components: B cells, T cells, phagocytic cells, or complement. An initial workup consists of complete blood count with differential (looking for lymphopenia, thrombocytopenia, or eosinophilia), immunoglobulin (Ig) levels (abnormal after infancy if IgG < 200 mg/dL, total Ig < 400 mg/dL, or absence of IgM or IgA), and antibodies to previously administered vaccines (children 2–5 years old should respond to at least 50% of the polysaccharide antigens). If any initial screening tests are abnormal, referral to a pediatric immunologist for definitive testing is recommended.³⁴

Conclusions

Our experience with this patient highlights the need to consider anaerobes as a

possible etiology for pulmonary empyemas, particularly when the patient does not appear to be responding to standard antimicrobial coverage. We identified *C rectus*, an anaerobic bacterium that exists in the human oral flora and is a known cause of periodontitis. Our case is an example that the known epidemiology of pediatric pulmonary infections is continuously changing.

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Hospital Pediatrics 2016;6;702

DOI: 10.1542/hpeds.2015-0274 originally published online October 14, 2016;

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DOI: 10.1542/hpeds.2015-0274 originally published online October 14, 2016;

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