Pneumonia in Children

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Alev Ketenci, Laura Gochicoa-Rangel, and Özge Yılmaz

79.1 Introduction

The most frequent reason for death in children worldwide who are under the age of 5 years is pneumonia. It is estimated that 808,000 children died due to pneumonia in 2017 (WHO), representing higher than five deaths to pneumonia per 1000 live births [1]. This child mortality disproportionately affects lower- and middle-income nations, but even in developed countries pneumonia still causes considerable morbidity and healthcare costs. Epidemiological research carried out in the USA ascertained a rate of 15.7 cases of community-acquired pneumonia per 10,000 children resulting in admission to hospital. The highest risk for this event was amongst children aged below 2 years [1–3].

Pneumonia refers generally to a situation in which the pulmonary tissues, particularly the alveoli, are inflamed. The characteristic symptomatic presentation in children is with fever, cough (productive or dry), and dyspnoea. The severity of clinical presentation may range from mild to severe, a number of pathogens can cause pneumonia in the paediatric age group: bacterial, atypical bacteria (especially *Mycoplasma pneumoniae*), fungal and viral [1–4].

Pneumonia may frequently be diagnosed with careful history and physical examination, with further investigations (chest X-ray, venous bloods, microbiological culture of sputum) helping to confirm the diagnosis. Pneumonia is often categorised

A. Ketenci (✉)
Section of Pulmonology, Başakşehir Pine and Sakura City Hospital, İstanbul, Turkey

L. Gochicoa-Rangel
National Institute of Respiratory Diseases, Mexico City, Mexico

Ö. Yılmaz
Division of Pediatric Allergy and Pulmonology, Department of Pediatrics, Faculty of Medicine, Manisa Celal Bayar University, Manisa, Turkey

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as community-acquired (CAP), nosocomial or healthcare-associated. If food or drink, vomitus or saliva is aspirated into the lungs, an aspiration pneumonia may also develop [1, 2].

Although pneumonia has high prevalence and is associated with significant burden to healthcare systems, correct and timely diagnosis as well as treatment may be challenging in many cases [1–4].

The main risk factors to present pneumonia in a child are presence of anatomical congenital abnormalities, immunological deficiencies, alterations of the mucociliary system, broncho-aspirations, prolonged hospitalisation, previous viral infection, neuromuscular disease, pain from trauma or surgery of the abdomen or chest, and artificial airway. Additionally, the risk increases if the patient is malnourished, has a low socioeconomic status, passive smoking, or go to nurseries or day care.

79.2 Aetiology

Isolation of the causative agent in paediatric pneumonia is not possible in most of the cases but viral aetiology accounts for more than 50% of cases. "Etiology of Pneumonia in the Community" [EPIC] is a population-based multicentre study carried out by the Centers for Diseases Control and Prevention using an active surveillance technique to identify cases of CAP. The results of this study showed that a viral pathogenic agent was the aetiology in 66.2% of CAP cases that necessitated hospital admission. The most common viral agents identified were respiratory syncytial virus (RSV, 28.0% of cases), rhinovirus (RV, 27.3% of cases) and human metapneumovirus (hMPV, 12.8% of cases) [1, 4, 5].

Pyogenic bacteria are not the common etiological agents of paediatric CAP but may be associated with severe disease and complications with high mortality. Pyogenic bacteria were implicated in 7.3% of paediatric pneumonia cases in the EPIC study. The most frequently isolated bacteria were *Streptococcus pneumoniae* followed by *Staphylococcus aureus* and *Streptococcus pyogenes*, with frequencies of 3.6%, 1.0% and 0.7%, respectively. *M. pneumoniae*, was isolated in 8% of cases of CAP, especially more frequently in children aged 5 and older [2, 4, 5].

The multicentre, prospective, observational cohort study, CHIRP (Children's Hospital's Initiative for Research in Pneumonia), enrolled 441 participants aged ≥2 months to 18 years old, diagnosed to have CAP. Both admitted patients and outpatients were enrolled (13.8% and 86.2%, respectively). The initial analysis of the data showed that a viral pathogen was present in 55.6% of cases, with 3.6% of cases caused by pyogenic bacteria and 8.8% by atypical bacterial organisms. The division of cases into viral and bacterial pneumonia was similar to that seen in the EPIC study [4, 5].

The PERCH (Pneumonia Etiology Research for Child Health) study involved 4232 paediatric patients under 5 years of age with pneumonia of marked severity in developing countries. The findings of the PERCH study concerning pathogen and epidemiological risk factors differed somewhat from those reported on CAP paediatric cases in advanced economies [4] Table 79.1.

Table 79.1 Bacterial pneumonia aetiology according to age

Age	Bacteria
Newborn	Group B Streptococcus Escherichia coli Klebsiella pneumoniae Listeria monocytogenes Proteus
1–3 months	Chlamydia trachomatis Group B Streptococcus Staphylococcus aureus Haemophilus influenzae Streptococcus pneumoniae
3 months to 5 years old	Streptococcus pneumoniae Haemophilus influenzae Staphylococcus aureus Mycoplasma pneumonia
Older than 5 years old	Streptococcus pneumonia Mycoplasma pneumoniae Staphylococcus aureus Haemophilus influenzae Moraxella catarrhalis Legionella pneumonia

79.2.1 Viral–Bacterial Interaction

The rate at which infections due to a virus and a bacterium co-occur in CAP has been reported as 7.0% (EPIC study) and 3.9% (CHIRP study). It is probable that these figures are underestimated due to the low sensitivity of bacterial detection methods used (such as blood culture). According to the EPIC study, concurrent viral and bacterial pneumonia cases were more likely to have high white cell count, pulmonary consolidation on chest X-ray, pleural effusion, intensive care admission with mechanical ventilation support and prolonged duration of hospitalisation [4]. One interaction of particular significance is co-infection by RSV and *S. pneumoniae* in IPD (invasive pneumococcal disease), which increases the severity and alters the likely outcome [6, 7].

Research using mice with a concurrent RSV and streptococcal pneumonia has shown that pulmonary inflammation is more severe, bacteraemia more common and death more common than either pathogen alone [8, 9]. A recent case-control study [9] compared the presence of potentially pathogenic bacteria (PPB) in nasopharyngeal swab cultures of children with bronchiolitis and healthy controls younger than 2 years age. Prevalence of PPB isolation was higher in the patients with RSV bronchiolitis than in the healthy children. Moreover, detection of *S. pneumoniae* or *H. influenzae* in the bronchiolitis group was associated with more severe disease. These findings point towards the potential role played by PBB within the upper respiratory tract in mediating the course and severity of pneumonia secondary to RSV [9] (Fig. 79.1).

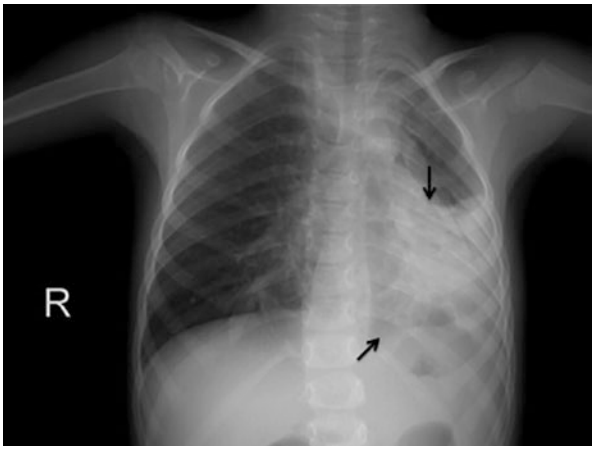

Fig. 79.1 Left lower lobe pneumonia in a 4-year-old girl with chest pain, fever and cough. Chest X-ray shows a large opacity (arrow) in the left mid and lower lung zones

79.3 Diagnosis

The clinical characteristics of pneumonia are fever, cough and dyspnoea. It is very important to identify if the patient is breathing fast (>50 breaths per minute in children from 2 to 12 months, >40 breaths per minute in those from 12 months to 5 years old and >30 breaths per minute in children older than 5 years), and if he/she has lower chest wall indrawing. Although, it is possible to diagnose pneumonia on the basis of the clinical presentation and chest X-ray, differential diagnosis especially from bronchiolitis in children may be challenging. The etiological microbiological agent cannot be isolated in majority of the subjects. Development of microbiological diagnostic methods with higher specificity and sensitivity may result in targeted pharmacotherapy, elimination of unwarranted investigations and perhaps lower morbidity and mortality [10] (Fig. 79.2).

The clinical presentation in paediatric cases of pneumonia secondary to atypical bacteria may resemble those of viral pneumonia, as may the results of laboratory testing and imaging. Indeed, pneumonia secondary to pyogenic bacteria may also present in a way that resembles viral pneumonia at the beginning, i.e. symptoms affecting the upper airways may predominate, inflammatory markers may not be very elevated and chest X-ray may reveal interstitial infiltrates [11]. Measurement of C-reactive protein levels and procalcitonin can be helpful in evaluation of treatment response when pneumonia is of high severity, but so far no clear cut-off value has been established that indicates the infection is of bacterial origin [10].

A further difficulty in identifying the causative agent in paediatric pneumonia arises from the fact that specimens for culture are challenging to procure from a child. Since pneumonia is a pulmonary condition, suitable specimens need to originate in the lung or the fluid contained within the alveoli. Thoracocentesis and bronchoalveolar lavage involve a high degree of invasiveness and are therefore not typically carried out in paediatric CAP cases. In younger children it is a challenge to procure a suitable sample for Gram staining and microbiological culture; hence

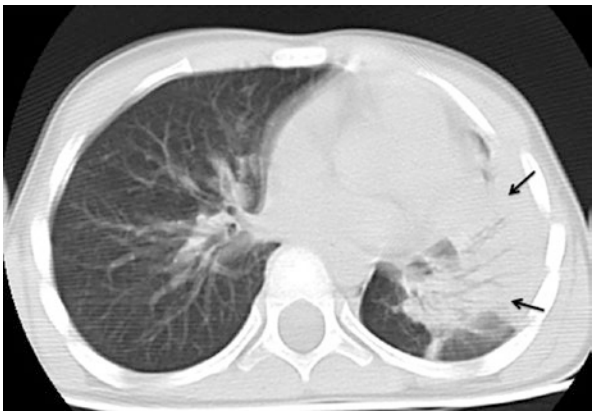

Fig. 79.2 Left lower lobe pneumonia in a 4-year-old girl with chest pain, fever and cough. Axial chest CT image with lung window settings demonstrates pulmonary consolidation with air bronchograms (arrows) in the left lower lobe (Courtesy of Esin Kurtulus Ozturk, MD)

these are not common investigations, either. Analysis of aspirate from thoracocentesis is of value in identifying causative pathogens, but in the majority of cases of CAP, there is insufficient fluid generated to permit aspiration. Thoracocentesis is therefore generally considered too invasive and the risk of complications too high. This leaves blood culture as the only feasible way of isolating pyogenic bacteria in paediatric CAP. However, it is a test of low sensitivity. Furthermore, since there seems to be an increased risk of co-infection with bacteria when a viral infection of the respiratory tract exists, isolation of a viral pathogen cannot preclude a bacterial aetiology also being present. Unfortunately, this situation frequently leads to clinicians over-employing antibiotic treatment and needlessly admitting patients to hospital [10, 11].

To diagnose *M. pneumoniae*, the method often employed is PCR (polymerase chain reaction) sequencing. Various researchers have cast doubt on the benefit to diagnosis of PCR sequencing [12], but it was considered a useful test by the researchers involved in the EPIC and CHIRP studies, applicable in various circumstances. If a viral aetiology is suspected in a child, nasopharyngeal swabs or aspirated fluid may be submitted for real-time PCR sequencing. However, it needs to be considered that PCR can also detect some of these viral pathogens in asymptomatic children and therefore the presence of viral pathogenic DNA need not prove aetiology. Viruses may persist for lengthy periods after resolution of an infection and may become active again following a different pathological event, especially rhinovirus or adenoviruses. It is unusual to detect other respiratory viruses, namely RSV, influenza or hMPV, unless symptoms of an infection are present [13].

Despite these limitations, being able to identify a viral respiratory pathogen in cases of paediatric CAP does offer assistance with management, since it is reasonable to withhold antibiotics if the clinical features, laboratory investigations and imaging results do not suggest co-occurring bacterial infection [11]. It is clear from the CHIRP study that the probability of being sent home from hospital and not started on antibiotic pharmacotherapy was higher in cases where there was proof of a viral aetiology and no evidence to support a bacterial aetiology [14].

79.4 Treatment

Pneumonia of bacterial origin without complications may be managed with oral antibiotic treatment on the outpatient basis. Provided a case of bacterial pneumonia is of no more than moderate degree, antibiotic therapy may be commenced empirically. There is no need to seek further investigations into aetiology unless there are other reasons to hospitalise the child. Possible reasons for admitting a child to hospital might be low oxygen saturation levels, moderate respiratory distress, age younger than 1 year and pleural effusion of at least moderate size. Moreover, lack of cooperation of the family and child for outpatient treatment and monitoring are relative indications for hospitalisation [15].

79.4.1 Outpatient Management

The vital element in treating cases effectively outside hospital is to find the most suitable antibiotic and the optimal dose. Treatment of choice depends on the probable etiological agent, the age of the child, contact with other cases, previous medical problems, drug allergy (if present) and the data available on local resistance patterns. Even though pneumococcal vaccination is now widespread, an agent needs to be chosen with activity against *S. pneumoniae*, as it is still the leading cause of bacterial pneumonia [16]. The treatment of choice currently is amoxicillin. Many clinicians tend to assume that per oral cephalosporin is a better choice to cover pneumococcal pneumonia, but this is an incorrect assumption. Whilst it is true that some strains of pneumococcus are penicillin-resistant, but are sensitive to ceftriaxone, cephalosporins given by mouth suffer from a brief half-life, low absorption from the gut, are predominantly protein-bound within the circulation and doses are frequently far apart. Accordingly, the concentration in plasma is inadequate to eradicate the pathogen, as can be seen by comparison of the plasma concentration and the usual minimum inhibitory concentration (MIC) for the pathogen, unless the strain has a low MIC. Oral amoxicillin, in comparison, achieves a greater plasma concentration and binds to protein to a lesser degree, which allows the MIC to be reached for a longer period. Amoxicillin is thus effective against pneumococci provided the bacterium is susceptible and the MIC achievable at an intermediate dosage level. Given the relatively unfavourable pharmacokinetic characteristics of cephalosporins versus amoxicillin, the former should only be used if the child has a penicillin allergy or the pathogen targeted is sensitive to cephalosporins but not amoxicillin, namely *M. catarrhalis* or an *H. influenzae* strain expressing a beta-lactamase [8, 17].

Another important element to consider when using beta-lactam antibiotics is the time between doses. It is not often appreciated that putting doses closer together can lengthen the “killing time” (i.e. period when plasma concentration exceeds the MIC), and thus be useful where a strain has a marginally higher than usual MIC. To give an illustration: suppose that the MIC for a certain strain of pneumococcus is 2.0 $mg.mL^{-1}$. If a dose of 90 mg/kg body weight is given b.d., this will eradicate the

organism in 65% of cases, whereas the same dose given t.d.s. will be effective in 90% of cases [18, 19]. Hence, to achieve a higher bioavailability a high dosage (between 90-100 mg/kg daily) should be administered t.d.s. rather than b.d. This rationale applies where strains of *S. pneumoniae* possessing resistance are prevalent or perhaps in any case of lobar CAP treated outside of hospital and where there is a risk of deterioration or complications [19]. The half-life of amoxicillin within ear fluid is longer than in the serum (4 h, rather than 1.2 h), which explains why treatment for otitis media is effective with b.d. dosing, whereas t.d.s. dosing is required for pneumonia of bacterial origin, since the killing time depends on the half-life of the drug at the site of action [20].

In the majority of cases, the antibiotic chosen empirically does not need to cover *H. influenzae* or *M. catarrhalis*. Where these pathogens are present, however, there is a 30% chance that *H. influenzae* will express a beta-lactamase, and all strains of *M. catarrhalis* do so. Thus, they will be resistant to amoxicillin. Generally, these organisms are sensitive to co-amoxiclav and cephalosporin agents. CAP may also potentially result from an infection of *S. aureus* or *S. pyogenes*, but the pneumonia that results is usually of a severity necessitating hospitalisation [15].

Diffuse and lobar CAP are sometimes due to infection by *M. pneumoniae*, but just how useful antibiotics are in this situation is still the subject of debate [21, 22]. The features of the history and findings on physical examination are an unreliable guide in distinguishing *M. pneumoniae* infections from other pathogens, which may result in unwarranted attempts to cover this organism. National guidelines advocate treating all children over the age of 5, but this may be unwarranted, since the benefits of this course of action are still not fully established. There needs to be clinical judgement used in interpreting advice from guidelines, rather than a blanket approach to treatment, which ignores cases where the pattern of symptoms fits a viral infection or another bacterium is already being treated. Attempts in adult patients to cover both typical and atypical bacterial infections have led to massive overemployment of fluoroquinolones, which the FDA is at pains to prevent [23]. Azithromycin has become the second most frequently used antibiotic by paediatricians treating non-hospitalised patients, who want to provide cover for more usual bacteria, alongside *Mycoplasma*. However, this agent has low efficacy against the more usual pathogens [24]. It has recently been proposed by researchers that the use of azithromycin in younger children has a protective effect on the later development of wheeze [25], but the research findings have some limitations and even if there is a clear advantage, the prescribing physician should also consider the downsides, in particular the hazards of dual treatment, higher burden of adverse effects, potentially contributing to bacterial resistance and the disturbance of the normal healthy microbial flora that results [26, 27].

Treatment courses for CAP lacking complications should last a maximum of 7 days, with evidence that a 3-day course is adequate in CAP of no more than moderate degree [28]. The benefit from a 7-day course has been shown to be similar to when a 10-day course was used, or even a 5-day course. Research concerned with treating CAP has a tendency to suffer from positivity bias (the so-called "Pollyanna phenomenon"), but the accumulating evidence gathered from trials of brief

treatment courses, taken alongside the advantages of shorter treatment durations (i.e. less development of resistant bacteria, lower adverse effect burden and greater patient concordance with treatment) ought to mean that a course of treatment between 5 and 7 days in duration becomes standard practice [29–31].

Treatment failure in cases of CAP treated outside hospital may be defined as a deterioration in clinical presentation in spite of treatment for two full days with an appropriate agent at the correct dose. Just because pyrexia is still present (generally, for 2 days more) [32], treatment failure should not be deemed to have occurred, provided other indicators (oral intake, slower respiratory rate, more participation in usual activities) point towards a clinical improvement.

79.4.2 Inpatient Management

There are two different categories of patients hospitalised for CAP. The first group consists of children who have pneumonitis of viral origin, in whom CAP may additionally have occurred. The second group consists of children in whom there is clear evidence of CAP of bacterial type, and some of whom also have a parapneumonic process. The first group of patients has been discussed earlier, and details are available in Table 79.1 about the diagnostic process, how they should be managed outside hospital and the criteria for admission. In the second group, with more straightforwardly diagnosed bacterial CAP, there are some key issues to bear in mind when treating. The first issue is the need to establish the aetiology through further investigations. The choice of antibiotic pharmacotherapy needs careful consideration, too, and any complications will need to be addressed [missing reference].

In a case of CAP where hospitalisation has occurred, the most likely aetiology is pneumococcal infection. However, in particular instances, other pathogens should be suspected. A child suffering from influenza, in whom CAP then develops, is likely to be infected with *S. aureus*. If there is rapid clinical deterioration, with or without indications of sepsis or toxic shock, the treating physician should suspect *S. aureus* or *S. pyogenes*. Ampicillin is efficacious in treating S. pyogenes, but some *S. aureus* strains are methicillin resistant (i.e. MRSA), the risk depending on the resistance characteristics in the area and how severe the disease is. It is still a matter of controversy whether treatment should provide cover for *H. influenzae* and *M. catarrhalis* in an admitted patient without immunodeficiency. Data comparing management in inpatients using ampicillin +/− amoxicillin versus the older use of broader spectrum agents indicates no major difference in benefit, even though the newer regimens do not cover 30% of *H. influenzae* strains or *M. catarrhalis* [33]. Parapneumonic processes have been observed in infection by *S. pneumoniae*, *S. pyogenes* and *S. aureus*.

All cases of bacterial CAP beyond those of mild degree result in inflammation, and research has focused on treatment to dampen down a florid inflammatory response. Macrolides and corticosteroids have been examined in this context. However, since there have been no studies up to the present involving the use of

steroids in children with CAP, a cautious approach is appropriate. In children with known asthma who develop CAP and whose airways show evidence of reversible obstruction, corticosteroid treatment for between 5 and 7 days is reasonable. Although azithromycin is a macrolide and thus potentially anti-inflammatory, currently it is not recommended to employ this agent in CAP.

79.4.2.1 Prevention

To reduce the morbidity and mortality from pneumonia, it is important to implement effective prevention measures, the main ones that has shown some evidence are: (1), immunisation against those organisms that causes pneumonia (H. influenzae type b, Pneumococcal conjugate vaccines, as well as measles, and pertussis); (2) adequate nutrition, undernutrition in children 0–4 years old contributes to more than one million pneumonia deaths per year; (3) exclusive breastfeeding, those under 6 months old who are not breastfed are at five times the risk of dying from pneumonia; (4) zinc intake has proven that helps to reduce the incidence of pneumonia and the severity of disease [34–38].

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