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Basic Concepts on Community-Acquired Bacterial Pneumonia in Pediatrics

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Abstract

Community-acquired pneumonia (CAP) is a common disease in infancy, requiring several pediatric specialties for its diagnosis and treatment. Establishing the causal agent of pneumonia is essential to guarantee the most appropriate and effective therapy and is pivotal to the development of therapeutic and preventive strategies. However, determining the etiology of pneumonia is still a challenge due to the relative inaccessibility of infected tissue and the difficulty in obtaining non-contaminated samples of the upper airway. Broncho alveolar lavage (BAL) yields adequate samples, but should be reserved for severe cases with poor outcome. Blood cultures should be obtained in all children in whom bacterial pneumonia is suspected. Serum samples should be collected during the acute phase and during convalescence as a preventive measure in case a microbiological diagnosis is not established during the acute period of the disease. Recent diagnostic advances have introduced the polymerase chain reaction (PCR), which in great measure has increased the ability to identify airway pathogens. Immunological markers provide information complementing clinical findings. New and more sensitive techniques should be evaluated to detect the etiological agents of severe pneumonia in children, particularly in developing countries.

Keywords: Acquired bacterial; Pneumonia; Pediatrics

Introduction

Community-acquired pneumonia (CAP) refers to the acute infection of the lung parenchyma in non-hospitalized patients; it is characterized by the development of fever and/or respiratory symptoms, as well as the presence of pulmonary infiltrates and consolidation on chest X-ray [1]. Ideally, the definition should include the isolation of the causal microorganism. However, the pathogen is not identified in a great number of cases, thus not fulfilling the clinical definition. CAP is classically classified into three syndromes: typical or bacterial CAP, atypical (due to viruses or atypical bacteria) and indeterminate (cases that do not fulfill the criteria required to include them in the first two groups). Oftentimes, it is difficult to clearly differentiate the types of CAP, so diagnostic algorithms have been developed based on the sum of clinical, analytic and radiographic criteria that may guide the diagnosis [2] (Table 1).

Table 1: Differential diagnosis between typical and atypical pneumonia.

Differential diagnosis between typical and atypical pneumonia [2]
1. Fever >39°C, sudden
2. Pleuritic chest pain (thoracic or epigastric)
3. Focal auscultation (rales, hypoventilation or tubal murmur)
4. Leukocytosis ≥12000/mm^3 with neutrophilia ≥6000/mm^3
5. Consolidation on chest X-Ray
Typical CAP: ≥3 criteria; Atypical CAP: 0 criteria; Indeterminate CAP: 1-2 criteria.

Clinical characteristics: bacterial CAP

In infants and small children, bacterial CAP tends to be the result of a previous viral infection, with low-grade fever that suddenly becomes a high-grade fever and worsening of the patient's overall condition. It may also manifest as fever of unknown origin, a "silent" pneumonia characteristic of pneumococcal CAP (Table 2).

Table 2: Synopsis of main recommendations.

Synopsis of main recommendations
Etiology and epidemiology

Streptococcus pneumoniae (*S. pneumoniae*) is the most frequent cause of bacterial pneumonia in childhood.
Age is a good predictor of probable pathogens:
Viruses are a more common cause in small children.
In older children, if a bacterial agent is found, it is more commonly *S. pneumoniae* followed by Mycoplasma and chlamydial pneumonia.
An important proportion of CAP (8-40%) is the result of a mixed infection.
Clinical characteristics
Bacterial pneumonia should be considered in children up to 3 years of age if fever is >38.5°C, retractions are present and respiratory rate is >50/min. In older children, a history of respiratory distress is more useful than clinical signs.
If wheezing is present in a toddler, primary bacterial pneumonia is improbable.
Radiographic findings
Chest X-Rays should not be routinely obtained in children with acute, uncomplicated lower respiratory tract infections.
Radiological findings are not good indicators of the etiology.
• Chest X-Ray follow-up is only useful after lobar collapse, apparent pneumonia or persistence of symptoms.
General testing
Pulse oximetry must be obtained in all children with pneumonia admitted to the hospital.
Acute phase reactants do not differentiate between bacterial and viral infections in children.
Microbiological testing
Specific microbiologic tests.
Blood cultures should be obtained in all children suspected of harboring bacterial pneumonia.
Obtain paired serum samples.
Severity evaluation
Indicators of hospital admission in babies:
oxygen saturation <92%, cyanosis;
respiratory rate >70 breaths/min;
respiratory distress.
Indicators of hospital admission in older children:
oxygen saturation <92%, cyanosis;
respiratory rate >50 breaths/min;
respiratory distress.
Management of antibiotics
Small children with mild symptoms of lower respiratory tract infection do not require treatment with antibiotics.
Oral amoxicillin is the first choice antibiotic in children under the age of 5 since it is effective against most pathogens causing CAP in this group, it is well tolerated and low-cost.
Since mycoplasma pneumonia is more frequent in older children, macrolide antibiotics may be used as empiric first-line therapy in children above age 5.
Complications
If a child remains febrile and in bad overall health 48 hours after admission, he should be re-evaluated while considering possible complications.

Etiology and Epidemiology

Pneumonia is responsible for 15% of all deaths in children under 5 years of age and accounted for 922,000 deaths in children in 2015.3 CAP is one of the most common infections in childhood, with a reported prevalence of 1,000 to 4,000 cases/100,000 children/year [3,4]. In the United States, CAP is the number one cause of death as a result of infection and the sixth main cause of overall deaths. Every year, it accounts for approximately 4.2 million ambulatory patient consultations and over 60,000 deaths [5].

CAP is not simple to manage. To establish an etiological diagnosis and initiate appropriate antibiotic treatment is frequently a complex task. Testing for CAP etiology is complicated due to the low yield of blood cultures [6], the difficulty in obtaining adequate sputum specimens and the reluctance to perform pulmonary aspirates and bronchoalveolar lavage in children. Quantifying the proportion of CAP due to bacteria is difficult. *S. pneumoniae* is supposedly, the most common bacterial cause of CAP but the microorganism is rarely identified in blood cultures.

The Pneumonia Etiology Research for Child Health (PERCH) Project refers to the complete and standardized multi-national evaluation of the etiologic agents leading to severe and very severe pneumonia in children in underdeveloped countries. PERCH will be the largest and broadest study on the etiology of childhood pneumonia conducted to date [7].

Diagnosis

Determining the bacterial etiology of pneumonia is a challenge, since access to the infection site (lung tissue) is complex and samples are difficult to collect. Samples from a sterile site are the “gold standard” in the diagnosis of invasive

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disease, but airway samples are more easily obtained in non-sterile sites.

A database should be established to support decision-making in terms of sample collection, considering the broad range of bodily fluids and tissue samples that could yield relevant data, the available clinical and laboratory resources in developing countries, patient safety, case-control studies and pathogen identification. Laboratory diagnoses are the cornerstone of any study on the etiology of pneumonia.

The routine laboratory evaluation of pneumonia patients still depends on methods that have been used for decades: microscopy and lower respiratory tract (LRT) samples, blood cultures, antigen detection in urine and respiratory samples, and the detection of specific antibodies in blood (serology) [8]. Nucleic acid detection methods, such as the polymerase chain reaction (PCR), have been available for over 2 decades and are now standard tools in tertiary level diagnostic laboratories.

PCR possesses many characteristics that make it an attractive tool for the diagnosis of airway infections [9]. This test can detect very low nucleic acid levels of all potential respiratory pathogens, it does not depend on the microorganism's viability, it provides results in a clinically timely manner and it is less affected by previous antibiotic administration than culture-based methods, and it can also indicate the presence of antibiotic-resistant genes.

Microscopy and culture

Microscopy and sputum or other LRT samples (bronchoalveolar lavage [BAL]) and blood cultures, have historically been the main diagnostic tools used to identify the microbial etiology of pneumonia. Respiratory pathogen identification in high quality samples directly obtained from the infection site or a normally sterile site (blood), provides good evidence on the probable causative agents.

LRT samples are generally cultured in standard microbiologic media such as the combination of blood, chocolate and MacConkey agars, isolating the most commonly found bacterial pneumonia pathogens. Some bacteria require special media (Legionella sp; buffered charcoal yeast extract-based media) or cells (Chlamydophila pneumoniae), or cannot be cultured in a diagnostic laboratory (Mycoplasma pneumoniae).

The process of sample collection is pivotal to microscopy and culture results as well as to their interpretation. LRT samples may become contaminated by upper respiratory tract (URT) secretions during collection or the collected sample may harbor URT secretions. The presence of <10 squamous epithelial cells (SEC) and >25 PMN per low power field (X 100) [10], or ≥10 leukocytes for every SEC [11], is indicative of a high quality expectorated sputum sample in adults. Sputum with relatively low numbers of PMN cells and a high number of SEC is highly suggestive of oropharyngeal contamination. However, the application of these criteria to sputum samples (including induced sputum) in children remains to be determined.

Samples for etiology determination

Pulmonary aspirates: From a diagnostic viewpoint, the ideal manner to determine the etiology of pneumonia hinges on the collection of a sample directly from the infection site (lung). Pulmonary aspirates are commonly used in the cytological search for malignancy but are also useful for infection detection. Some centers may be unable to perform pulmonary aspirates due to restrictions of a practical nature (limited availability of a radiologist or radiographic equipment). The technique can be used in settings with careful monitoring capacities (close nursing observation, pulse oximetry and chest X-Ray availability) and efficient management of complications (intubation equipment and experience).

LRT secretions: In children with pneumonia, LRT secretions are of diagnostic importance because these samples originate in the site of infection and may be obtained non-invasively in most cases. It is difficult for children to expectorate because they tend to swallow secretions, so the use of BAL or sputum induction may be necessary to collect a LRT sample. In order to obtain the sample by BAL, the bronchoscope is placed in the bronchus of the radiologically compromised pulmonary segment and variable volumes of sterile physiological solution are instilled in quantities varying between 20 and 100 mL. After every instillation, the fluid is aspirated to recuperate the maximum volume possible, which includes a mixture of physiological solution and bronchoalveolar secretions. In order to establish the diagnosis, quantitative cultures are performed by serial dilution; growth above 104 ufc/mL is considered significant, since this number of colonies in a milliliter of secretions and diluted in 10 to 100 milliliters of aspirated physiological solution, represent between 105 and 106 ufc/mL in the original sample. However, this criterion is subject to discussion since the degree of dilution of alveolar material in the instilled solution is unknown.

Quality control of the sample's suitability should be performed: it consists of a new differential cell count after Giemsa or Gram staining of the obtained extensions after sample centrifugation and in which no squamous cells should be observed in a proportion equal to or greater than 1% of the total counted cells, which must be 300. If this number is exceeded, contamination of the sample by URT microorganisms is almost certain and the culture results should be questioned. The diagnosis is favored when intracellular bacteria are observed after Gram staining in an extension obtained after centrifuging the sample, and it can be considered diagnostic if microorganisms are observed in 5% or more cells (sensitivity, close to 70% and specificity, above 90%).

Bronchoscopy is not a routinely used technique in CAP since most cases follow a favorable course. It is reserved for severe cases or with poor outcome [12], and/or persistent radiological anomalies or recurrent pneumonia in the same site. Overall, the indications for bronchoscopy in pediatrics are quite well established [13]. If used for diagnostic purposes, as in the case of CAP, it is usually associated to BAL thus allowing the collection of samples for analysis. The sensitivity and specificity of the collected samples vary in function of the causal microorganism, the employed technique and the child's degree of immune

suppression. The isolation of potentially pathogenic microorganisms leads to the assumption that they are the etiological agent of the pneumonic process, but the isolation of others may only mean they are airway commensals or contaminants.

When no previous pathological history is present in immunocompetent children, severe pulmonary infection warranting intensive care, require evaluation of the associated inflammation and the identification of the causal agent and in this case, bronchoscopy and BAL are justified [14]. Bronchoscopy and BAL are both safe diagnostic techniques that can be used in children of any age and in any condition. Complications are minimal and transient (desaturation, coughing spells, increased fever). The diagnostic usefulness of BAL (with or without bronchoscopy) has been documented in intensive care units, particularly in the diagnosis and management of ventilator associated pneumonia [15]. However, due to the possible need of mechanical ventilation, the need for anaesthesia or sedation of the children before the procedure, the need for trained clinicians and the support system to ensure the patients' safety, BAL is not an ideal method when evaluating CAP in infants and children with scarce resources.

Sputum induction is the most often used method to diagnose pneumonia in settings with a high prevalence of tuberculosis and in children with cystic fibrosis. It has also proven useful in hospitalized children with CAP [16]. In spite of a meticulous technique, pharyngeal contamination commonly occurs and the results of bacterial cultures and induced sputum nucleic acid detection tests must be carefully interpreted in order to determine whether a potential pathogen is a contaminant from the URT or the cause of LRT disease. The availability of induced sputum and pulmonary aspirate paired samples in the PERCH study will test the validity of induced sputum as a diagnostic test.

Pleural fluid: Diagnostic tests in pleural fluid may be useful in children with pneumonia complicated by a pleural effusion. The sample collection technique is well established and is routinely used in clinical medicine.

Upper respiratory tract (URT) samples: The oropharynx (OP) and the nasopharynx (NP) are the 2 most common ports of entry of microorganisms in the URT. However, the detection of a pathogen in the URT is not sufficient proof that it is the cause of pneumonia.

Blood samples: A number of tests can be performed in blood when diagnosing pneumonia. Although blood cultures are positive in a minority of children hospitalized with pneumonia (low sensitivity, <20-30%), those microorganisms that are indeed identified in blood culture are widely accepted as indicative of the pneumonia's etiology and the results of their antibiotic sensitivity should guide therapy [17]. The blood culture yield could be improved by carefully determining the inoculated blood volume, minimizing sample contamination, optimizing storage and transportation, being watchful of the incubation conditions and guaranteeing the personnel's appropriate capacity to evaluate the bottles with positive cultures.

Acute phase serology or paired acute/convalescent samples were among the first techniques developed for the diagnosis of pneumonia and are still in use to date [18]. Serology may be useful when detecting fastidious pathogens and may provide further support when establishing an association between an URT pathogen and pneumonia.

Additional blood work that may provide information when diagnosing pneumonia include the evaluation of risk factors (malaria, hemoglobinopathies, HIV infection) as well as biomarkers (C-reactive protein, procalcitonin). Withdrawal of a small blood volume is of minimal risk to patients. A maximum of 3 mL/K in 24 hours is recommended although further care should be taken in children with anemia or decreased blood volume.

Urine samples: Several infectious causes of pneumonia can be detected with urinary antigen tests. Although they can be used to diagnose pneumococcal pneumonia in adults, they lack specificity in children due to the high prevalence of pneumococcal colonization in childhood.

Post-mortem lung tissue samples: Identifying the cause of deadly pneumonia is critical to the understanding and prevention of pneumonia-related deaths; however, there are many cultural and social limitations to post-mortem examinations in many countries. Immediate post-mortem percutaneous lung biopsy provides a simpler and less invasive method to obtain pulmonary tissue.

Storage and transportation

Ensuring the quality and standardization of sample transportation, storage and laboratory testing is fundamental to a successful diagnosis.

Immunological factors

Childhood pneumonia, particularly CAP, is an infection that may become severe and although its incidence has decreased up to 25%, it is still one of the most frequent causes of death in childhood. Early empirical therapy is necessary due to its high mortality. In 2012, childhood pneumonia and diarrhoea killed approximately 1.7 million children under the age of five [19].

A simple explanation hinges on the physiological immaturity of the immune system of neonates and hence, their proclivity to infection [20] Thus, the fetus and the neonate are more vulnerable than older infants and adults to contract severe infections from a broad array of pathogens, including pyogenic bacteria, viruses, fungi and intracellular protozoa [21]. Hence, it is difficult to obtain representative samples in CAP, in infants severe cases or with poor outcome, [12] and in whom various possible etiologic agents are obtained by bronchoalveolar lavage; the diagnosis and treatment of childhood pneumonia is challenging and further compounded by our lack of knowledge on the reasons why some cases become severe or very severe. We know for a fact, that there are substantial limitations to innate and adaptive immunity in the prenatal and postnatal periods that tend to disappear as the individual grows and the immune system matures.

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The deterioration of T cell neonatal immunity is evidence of decreased immune capacity and has been proven with the results of hematopoietic stem-cell transplants; if allogeneic umbilical cord hematopoietic cells are transplanted, the risk of developing acute graft-versus-host disease is low. This entity is mainly mediated by donor naive T cells while in bone marrow and peripheral blood transplants, adult T cells are differentiated [21]. Clinical observations such as the aforementioned have emphasized the importance of physiological immaturity in the fetal, neonatal and infant phases, in terms of the severity of contracted infections during those stages and may partially explain some of the variables leading to CAP and a severe or very severe course.

The normal immune system protects the individual from myriad of potentially pathogenic microorganisms and also prevents injury against its own constituents; this results from the effects of an intricate network of cytokines that regulate the immune system's cellular interactions. The study of cytokines is clinically relevant since they can provide a diagnosis, treatment guidance and preventive measures of infectious disease, as does the study of antibody effects and complementary systems (such as the classic and alternate complement systems and the lectin system). The study of the actions and concentration of these immune response mediators in their dynamic interaction with infectious microorganisms, may lead to markers of the severe inflammatory response as seen in childhood bacterial CAP, and may help us understand the different degrees of infection severity and their management.

Although the maturity of the immune response is different in adults and children, immune markers may display the same activity in both populations with CAP; for instance, Interleukin-6 (IL-6) and granulocyte colony-stimulating factor (G-CSF) levels are increased in both adults [22] and children [23]. However, the concentrations of pro-inflammatory and anti-inflammatory cytokines in the plasma of children with pneumonia, were higher in children with severe disease. There is evidence that G-CSF and IL-6 can provide complementary information on the infection's severity [23]. These same authors established that pro-inflammatory cytokines were significantly higher in the plasma of children with severe pneumonia; those with non-severe pneumonia had increased concentrations of Interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α). Among the cytokines capable of down-regulating the production of pro-inflammatory cytokines, a significant difference was found, whereby Interleukin-4 (IL-4) concentrations were higher in patients with severe pneumonia when compared with the non-severe pneumonia group; however, there were no significant differences in Interleukin-10 (IL-10) concentrations, a predominantly anti-inflammatory cytokine. These studies complement those by Paats MS [24] that concluded that the pro-inflammatory cytokines IL-6 and Interferon-gamma (IFN-γ), as well as the anti-inflammatory cytokine IL-10, could be markers of CAP disease severity since they were elevated in his study.

However, both of these studies as well as others [25-27] must be cautiously interpreted since many factors must be taken into consideration when evaluating the results, such as the difficulty in determining normal cytokine values according to the population's age, including the appropriate "normal" control subjects, and accounting for the negative correlation of some cytokines with age (the production of cytokines such as IL-6 and TNF reach adult levels in the first three years of life, while IFN-α and IL-12 concentrations may remain low until adolescence) [20,28].

Although characterizing the immune response on the basis of cytokine production in acquired pneumonia can foster our understanding of the infected host's immune response, we are still far from being able to diagnose CAP or establish a prognosis based on cytokine production. There are however, demonstrated immunological similarities between adult and childhood CAP whereby the study of a single cytokine can confidently differentiate the etiology of pneumonia [29] and an elevated IL-6 concentration may be a biomarker reflecting the severity of pneumonia in children and adults [30]. Without applying immunological knowledge, understanding the pathogenesis and pathophysiology of infectious disease cannot be clearly understood, but in the case of CAP in pediatric populations, important advances have allowed us to focus on diagnostic strategies, since plasma concentrations of pro and anti- inflammatory mediators (cytokines) are greater in children with severe pneumonia than in those with non-severe cases, reflecting the degree of immune activation in both groups. The cytokines that are usually affected in pediatric CAP are IL-6 and G-CSF.

Conclusion

In conclusion, when there is a positive response to oral antibiotic treatment, analytic and radiographic studies are not required. If there is no initial clinical response, the patient should be evaluated in the hospital and further basic ancillary studies should be obtained (Chest X-Ray, complete blood count, ESR, PCR, Monteux test) to determine whether hospitalization is warranted. Bronchoscopy is not routinely required in NAC since most cases evolve favourably. It is reserved for severe cases and a torpid course. Immunological marker determinations provide supplementary information to the clinical findings, but are not pivotal to the determination of the pathogen causing pneumonia.

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