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Community-acquired pneumonia in children: Current challenges and future directions

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Summary Pneumonia is a commonly encountered illness and the leading cause of death in children under 5 years of age. Our current management strategies remain less than optimal in part because we do not have adequate tools to determine etiology, classify patients and predict their outcomes. Studies in the last decade have demonstrated that viruses are commonly detected in children with pneumonia, but on many occasions this is not sufficient to establish a clear etiologic diagnosis since bacterial coinfection cannot be excluded. Gene expression profile analysis provides a comprehensive assessment of the host response to infection. Preliminary data suggest that transcriptional profile analysis and measurement of Molecular Distance to Health (MDTH) scores allows more precise patient classification than current diagnostic techniques and laboratory markers. Application of this tool to the evaluation of children with pneumonia may enhance our clinical decision making process and ultimately improve patient outcomes.

The burden of pneumonia in children

Worldwide pneumonia is the leading cause of death in children under 5 years of age.[1] Annually, more than 25% of children in the developing world will have an episode of pneumonia during the first 5 years of life and there are greater than 1.9 million deaths per year.[2] In industrialized countries, pneumonia has an annual incidence of 36—40 per 1000 children below the age of 5 years and 11—16 per 1000 in children 5—14 years of age.[3] Although mortality does not reach the levels seen in the developing world, there is still significant morbidity and financial burden

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associated with pneumonia. There are an estimated 2.5 million cases annually in Europe and in the United States it is second only to injuries as the most common reason for hospitalization in children less than 18 years of age.[4]

Despite the fact that it is a commonly encountered illness, the optimal management of children with community-acquired pneumonia (CAP) remains unknown. First, a specific etiology is not identified in many cases,[3,5–10] making targeted therapy difficult. In some cases this may lead to inappropriate interventions including excessive treatment with antibiotics and unnecessary hospitalizations. Additionally, appropriate triage of children with CAP can be problematic as clinical features are neither specific nor consistent[11] and there are currently no reliable tools that can be used to classify and predict which patients will develop complications or need a higher level of care. Moreover, there are no strict criteria for hospitalization and the decision to provide inpatient care is often based on the experience of the clinician.

The ability to accurately identify patients with CAP at higher risk for complications could assist clinical decision-making in a number of ways: 1) determining the need for hospitalization, 2) determining the type and route of antibiotic administration or whether withholding antibiotic treatment is reasonable, and 3) suitability for discharge in hospitalized patients. This could lead to decreased use of antibiotics and potentially play an important role in slowing antibiotic resistance, lowering healthcare costs, and reducing the number of adverse events associated with antibiotic use and hospitalization.

Diagnostic dilemmas

Determining which child has pneumonia is often the initial challenge for many clinicians. First, there is no single diagnostic definition for CAP in children. Second, the clinical features are non-specific and overlap significantly with other respiratory diseases making it difficult to differentiate those with pneumonia from bronchiolitis or even asthma,[12,13] though each of these conditions are treated quite differently. Not only do signs and symptoms not distinguish between pneumonia and other disorders, they also cannot discriminate between a viral or bacterial process once a diagnosis of CAP has been made.[11]

Imaging is often used to confirm the diagnosis of CAP or to determine the extent of disease. While chest radiographs can be helpful in this regard, they have limited value in discerning between viral and bacterial etiologies.[14] There is some evidence that performing a chest x-ray may decrease excess antibiotic use in children with clinically suspected pneumonia,[15] although radiographs may also lead to overdiagnosis of pneumonia in patients with other lower respiratory tract conditions and associated abnormal x-rays.[16] Conversely, a chest x-ray may be normal early in the course of pneumonia, leading to delayed diagnosis.

Many studies have examined the utility of inflammatory markers, such as peripheral white blood cell (WBC) count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and procalcitonin (PCT), in the diagnosis of pneumonia. Thus far, they have been shown to have a limited role, as it is a difficult to find a cutoff for any of these values that is both sensitive and specific. If one or more of these values is significantly elevated, a bacterial etiology is more likely, although normal or minimally elevated values do not exclude it.[6,14,17,18] Thus, we still lack an accurate diagnostic test or algorithm for CAP in children.

Etiology of pediatric CAP

Once the clinician determines that a child is suffering from pneumonia, pathogen detection remains a significant challenge. The laboratory assays and radiologic techniques currently used in clinical practice do not allow a precise etiologic diagnosis. If a combination of multiple microbiologic techniques is used, a potential etiology for CAP can be discovered in up to 86% of hospitalized children,[3,5–9] although this number is often lower in ambulatory patients.[9,10]

In studies using serology and direct fluorescent antibody (DFA) assays, viruses have been implicated as the sole etiology in 19–33% of cases in children.[3,6,8,9] This percentage is even higher when considering those less than 2 years of age.[3,8] However, recent advances in molecular diagnostic assays have dramatically improved our ability to diagnose viral respiratory infections and advanced our understanding of the impact of respiratory viruses in pediatric CAP. With the use of polymerase chain reaction (PCR) assays viruses have been found in up to 88% of children hospitalized with CAP[19] and up 83% of those less than 18 months old.[20]

While progress has been made in viral diagnostics, this has not been the case for common bacterial pathogens, where we still rely heavily on traditional culture techniques. Blood cultures, while very specific, are only positive in up to 11% of hospitalized children with uncomplicated CAP,[21] with some studies reporting positivity rates less than 3%.[3,22,23] This number may be even lower in those treated as outpatients.[24] Additionally, reliable specimens from the lower respiratory tract are not readily available in the pediatric population. While sputum cultures are easily acquired in adults, it is difficult to obtain quality sputum from children. Data from lung tap studies in various areas of the world show bacterial pathogens can be detected in 32–66% of children with CAP.[25] However, this method of pathogen detection is invasive and often not feasible in the routine clinical setting. Serology is available for many bacterial and viral pathogens but the accuracy varies widely and the need for both acute and convalescent samples limits utility in many cases.

Studies report concomitant detection of viruses and bacteria in up to 30% of children with CAP.[3,8,9] However, given the limitations in bacterial detection, the true incidence remains unknown. Therefore, optimal management of children with one or more respiratory viruses is unclear. In the appropriate clinical setting, the identification of a viral pathogen in respiratory secretions may be enough to establish the diagnosis. In other cases, however, the presence of a respiratory virus, even when there is no bacterial pathogen identified, is not sufficient to establish a clear etiologic diagnosis since bacterial coinfection cannot be excluded.

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Challenges in the management of children with CAP

Treatment of children with CAP presents another dilemma for clinicians. Given the significant role of viruses in CAP in children, some experts have suggested that withholding antibiotics should be considered in children who appear only mildly ill when a viral etiology is suspected.[26,27] However, given the lack of clinical features and laboratory data to reliably differentiate viral from bacterial infection, this is not often done in practice, with up to 98% of children with pneumonia receiving antibiotics.[28,29] Many children with viral infections may be receiving unnecessary antibiotics, a contributing factor in the emergence of antibiotic resistance.[30]

Another apparent gap in the management of children with CAP is the inability to accurately classify or predict disease severity. Severity scoring systems have been developed and validated for adults with lower respiratory tract infection but such tools do not exist for children. While there are some well-defined criteria for hospitalization of children with CAP[27] there is also a subjective component, with the decision to provide inpatient care relying heavily on the judgement of the clinician. More accurate and rapid identification of those children at higher risk may allow enhanced determination of the need for hospitalization, faster initiation of appropriate antimicrobial therapy, and ultimately improved clinical outcomes.

Novel strategies for diagnosis and management

Given the obstacles described above, it is clear we need to reexamine our approach to the diagnosis and management of children with pneumonia. To this end, it is essential to define both the microbial pathogen(s) responsible for the infection and the host immune response to the pathogen(s) better. In preliminary studies, analysis of host gene expression profiles, in combination with comprehensive microbiologic diagnostic assays, has shown promise in allowing a more precise diagnosis and better assessment of clinical disease severity in this patient population.

Gene expression profiles of peripheral blood leukocytes have demonstrated the ability to differentiate viral from bacterial infections with 95% accuracy, and to identify unique profiles in patients with bacterial and viral respiratory tract infections.[31] Our preliminary studies demonstrate that application of gene expression profile analysis to children with CAP can significantly enhance our ability to classify patients according to the class of pathogen causing the infection,[32] and more importantly according to disease severity.[33]

Molecular distance to health (MDTH) is a novel and unbiased metric that summarizes in a single score the data derived from whole gene expression analyses and provides a global assessment of the perturbation of the patient immune profile compared to healthy controls.[34] It has been shown to accurately classify the severity of the disease in patients with bacterial sepsis,[34] staphylococcal infections,[35] as well as in children with respiratory viral infections.[36] When applied to hospitalized children with CAP, this score correlated with clinical surrogates of disease severity, such as length of hospitalization, days of fever, and days of respiratory symptoms, as well as commonly used laboratory markers, C-reactive protein and procalcitonin.[33]

Developing tools and/or biomarkers that allow accurate patient classification by etiology and disease severity will result in prompt, more appropriate and targeted therapies, which in turn will lead to improved clinical outcomes. By bringing these tools to the clinical realm and making them readily available for real-time decision-making, we have the unique opportunity to change the paradigm of how we diagnose and care for patients with pneumonia.

Conflict of interest

None declared.

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