Curr Infect Dis Rep (2014) 16:451
DOI 10.1007/s11908-014-0451-8

RESPIRATORY INFECTIONS (F ARNOLD, SECTION EDITOR)

Biomarkers for Community-Acquired Pneumonia in the Emergency Department

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Published online: 28 October 2014

Abstract Community-acquired pneumonia is one of the most common reasons for emergency department (ED) visits in children and adults. Despite its prevalence, there are many challenges to proper diagnosis and management of pneumonia. There is no accurate and timely etiologic gold standard to differentiate bacterial from viral disease, and there are limitations with precise risk stratification of patients to ensure appropriate site-of-care decisions. Clinical factors obtained by history and physical examination have limited the ability to diagnose pneumonia etiology and severity. Biomarkers offer information about the host response to infection and pathogen activity within the host that can serve to augment clinical features in decision-making. As science and technology progress, novel biomarkers offer great potential in aiding critical decisions for patients with pneumonia. This review summarizes existing knowledge about biomarkers of host response and pathogen activity, in addition to briefly reviewing emerging biomarkers using novel technologies.

This article is part of the Topical Collection on *Respiratory Infections*

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Keywords Community-acquired pneumonia · Biomarkers · Leukocyte count · C-reactive protein · Procalcitonin · Proadrenomedullin · Diagnostic testing · Blood cultures · Sputum cultures · Polymerase chain reaction · Emergency medicine · Transcriptomics · Metabolomics · Pediatric · Adult

Introduction

Community-acquired pneumonia (CAP) causes substantial morbidity and mortality worldwide [1, 2]. The Infectious Diseases Society of America (IDSA) has published guidelines on the management of CAP in adults and children, including recommendations regarding diagnostic testing. There are several important differences between the two guidelines. For example, in adult patients requiring the intensive care unit (ICU) or who fail outpatient therapy, the guideline recommends performing a blood culture and a sputum culture, in addition to legionella and pneumococcal urinary antigen tests [3••]. Although performing blood cultures is recommended in children with pneumonia as well, additional recommendations, such as testing for influenza and *Mycoplasma pneumoniae*, are also recommended to guide antimicrobial therapy [4••]. These differences in recommendations stem from several key distinctions between children and adults, including differences in pneumonia etiology, differences in bacterial colonization rates, and the inability in obtaining quality sputum samples in children.

Despite these guidelines, there is substantial variation in the emergency department (ED) management of CAP [5–8]. This emphasizes the need for improved diagnostics for CAP that at the very least differentiate between viruses and bacteria and potentially all of the etiologies found in the adult and pediatric population. In addition, improvement in the ability to risk stratify patients with CAP is needed to enable effective site-of-care decisions. In adults, several clinical severity scores

have been developed to guide clinicians in predicting clinical outcomes; however, these are limited by their complexity or their moderate ability to predict clinical outcomes other than mortality [9, 10]. Unfortunately, such validated clinical scores do not yet exist for children with CAP. Biomarkers therefore offer the potential to improve clinical decision-making around CAP etiology and severity beyond clinical scoring systems.

A biomarker is defined by the National Institutes of Health as a characteristic (e.g., protein, metabolite, etc.) that is an indicator of a biological process, either normal, pathogenic, or as a response to a therapeutic intervention [11]. Biomarkers for CAP, such as white blood counts, procalcitonin, and C-reactive protein, have been suggested as potential aids in the differential diagnosis of pneumonia and the decision whether to initiate antibiotic therapy [12, 13]. Biomarkers for CAP can be classified as those released by the host in response to the infection, such as inflammatory markers, and those that measure pathogen activity within the host, such as cultures and organism load. By assisting with etiologic diagnosis or providing information about disease severity or prognosis, these biomarkers may be useful in the management of patients with CAP in the ED [13, 14]. It is critical to recognize that biomarkers are not a substitute for a carefully performed history and physical examination, that biomarker results are completely dependent on being performed with appropriate clinical suspicion and using sensitive and specific assays, and that it is highly likely that no single biomarker in isolation will accurately provide all the information necessary for accurate clinical care. However, biomarkers offer great potential in providing adjuncts to and augmenting the clinical examination for CAP diagnosis and management.

Biomarkers of Host Response to Infection

Leukocyte Count

Traditionally, an elevated leukocyte count was considered to be associated with a serious bacterial infection (SBI), including CAP. However, a recent meta-analysis found that leukocyte count was less valuable for ruling in SBI than inflammatory markers such as C-reactive protein (CRP) or procalcitonin (PCT) and that it was not useful for ruling out SBI [15]. Although leukocyte count is more likely to be elevated in children with CAP compared with adults [16], recent data suggests that leukocyte count is not useful in the majority of children diagnosed with CAP [4••]. Furthermore, multiple studies suggest that leukocyte count is of no value in differentiating viral from bacterial etiology of CAP in children or adults [17–25].

The IDSA/American Thoracic Society (ATS) guidelines for management of adults with CAP recommend that the use of diagnostic tests to identify an etiologic diagnosis of CAP in outpatients is optional. For inpatients, the guidelines recommend testing for specific pathogens under specific conditions, but leukocyte count is not one of the explicitly recommended tests (Table 1). The IDSA/Pediatric Infectious Diseases Society (PIDS) guideline for the management of childhood CAP concludes that the specificity of the leukocyte count in making the diagnosis of bacterial pneumonia in children is poor and that although leukocyte count may be elevated in children with bacterial pneumonia, the degree of elevation does not distinguish between viral and bacterial pneumonia [4••, 24]. Because of its lackluster diagnostic performance, the guideline recommends avoidance of routine measurement of leukocyte count in outpatients, while it is tentatively recommended in those with severe disease to be interpreted in context of other laboratory or imaging studies (Table 1) [4••].

C-Reactive Protein

CRP is an acute phase reactant largely produced by the liver in response to interleukin-6, a cytokine released at sites of inflammation [26]. CRP has been shown to have limited value in differentiating pneumonia from other respiratory conditions. In adults, a CRP value >48 mg/L distinguished pneumonia from asthma exacerbations with 91 % sensitivity (95 % confidence interval (CI), 80–97 %) and 93 % specificity (95 % CI, 86–98 %) [27]. In children, an elevated CRP, particularly greater than 100 mg/L, was associated with radiographic pneumonia with a positive likelihood ratio of 7.3 and positive predictive value of 88 %. Despite these findings, almost one-third of children with pneumonia had a CRP below 20 mg/L with a negative predictive value of 72 %. Therefore, CRP alone should not be used to diagnose pneumonia, but it may have some utility in combination with other clinical features and biomarkers.

There have been conflicting results about the ability of CRP to predict a bacterial etiology of CAP. A recent meta-analysis of 8 studies and more than 1200 children found that CRP values greater than 40–60 mg/L were a weak predictor of bacterial etiology in children with CAP. This meta-analysis included studies that had significant heterogeneity, particularly around definitions of bacterial pneumonia. Even with a pooled odds ratio of 2.58 (95 % confidence interval, 1.20–5.55), the positive predictive value of CRP >40–60 mg/L in predicting bacterial etiology was only 64 % [28]. Given these limitations, CRP should not be used to predict bacterial pneumonia in children [4••, 13, 29]. Similar limitations of CRP are seen in adults with CAP [30].

With regard to clinical outcomes and disease severity, several studies in adults have demonstrated that CRP on presentation and CRP kinetics measured over the course of a hospitalization (i.e., failure of CRP value to fall during hospitalization) were associated with adverse clinical outcomes, including ICU admission and elevated pneumonia severity

Table 1 Infectious Diseases Society of America recommendations for laboratory diagnostic testing in community-acquired pneumonia

Diagnostic test	Adult recommendations [3••]	Pediatric recommendations [4••]
Host response		
Leukocyte count	Not mentioned	Routine measurement NOT recommended; may assist in those with severe disease
C-reactive protein	Not mentioned	Cannot be used as sole determinant to distinguish viral vs. bacterial disease; do NOT routinely obtain, but may be helpful in more serious disease, particularly to track resolution
Procalcitonin	Not mentioned	Cannot be used as sole determinant to distinguish viral vs. bacterial disease; do NOT routinely obtain, but may be helpful in more serious disease, particularly to track resolution
Proadrenomedullin	Not mentioned	Not mentioned
Pathogen activity		
Blood culture	Severe disease, ICU admission, cavitary infiltrates, leukopenia, alcohol abuse, chronic severe liver disease, asplenia, positive pneumococcal antigen result, pleural effusion; optional for other hospitalized patients	Failure of antibiotic therapy, progression of disease despite antibiotic therapy, moderate to severe disease requiring hospitalization
Sputum culture	ICU admission, intubated patients (endotracheal), failure of outpatient therapy, cavitary infiltrates, alcohol abuse, severe obstructive/structural lung disease, positive pneumococcal or *Legionella* antigen result, pleural effusion	Hospitalized patients who can adequately produce sputum
Pleural fluid Gram stain and culture	If pleural effusion >5 cm present	If pleural fluid specimen obtained
Mycoplasma pneumoniae and *Chlamydophila* testing	Not mentioned	Obtain *Mycoplasma* testing in those with suspected atypical pneumonia; *Chlamydophila* testing NOT recommended
Influenza testing	Obtain if likely to change management	Sensitive and specific tests for influenza recommended during influenza season
Other viral testing	Not mentioned	Consider if clinical decision-making will be altered by result
Legionella urine antigen	ICU admission, failure of outpatient antibiotic therapy, alcohol abuse, travel within the past 2 weeks, pleural effusion	Not mentioned (*Legionella* not a major pathogen in children)
Pneumococcal urine antigen	ICU admission, failure of outpatient antibiotic therapy, leukopenia, alcohol abuse, chronic severe liver disease, asplenia, pleural effusion	Not recommended
Polymerase chain reaction	Not mentioned	Pleural fluid PCR test for *Staphylococcus aureus* and *Streptococcus pneumonia*

index scores, though not with mortality [31–36]. Despite this association, PCT was more strongly associated with these outcomes than CRP [30, 32, 37, 38], and therefore, PCT may be of more value than CRP (see below). Furthermore, there are discordant results with regard to the associations of CRP and these outcomes, suggesting that CRP may not be useful for determining the prognosis of adult CAP [38]. These conflicting results emphasize the need for continued research to determine the optimal combination of clinical factors and biomarkers for risk stratification.

Procalcitonin

PCT is a 116-amino acid peptide precursor of the thyroid hormone calcitonin [39]. PCT is derived primarily from nonthyroidal tissues and is typically not detectable at high

levels (<0.1 ng/mL) in the serum of healthy subjects. PCT expression and secretion are stimulated in various inflammatory and infectious conditions [40], but circulating levels are particularly elevated in severe bacterial infection, sepsis, and multiple organ dysfunction [41]. PCT is being increasingly used as a diagnostic, prognostic, and therapeutic biomarker in CAP [42], particularly as assays become more efficient and rapid bedside tests are developed. It is important to recognize that the accuracy of PCT and its optimum cutoffs are fully dependent on the use of a sensitive assay in a specified clinical setting with a pretest probability for the presence of a specific infection. Commercially available assays have functional sensitivities as low as 0.06 mcg/L, and results can be obtained within 1 h using 20–50 μl of plasma or serum [43]. An additional caution in the use of PCT is that it can be elevated in noninfectious conditions, such as severe trauma, pneumonitis, and burns, and similarly can remain low in bacterial sepsis.

Adult Studies

In the ED setting, PCT has been shown to be of value in the diagnosis and prognosis of adults with CAP. As a diagnostic biomarker, PCT has been shown to assist in the diagnosis of pneumonia when the diagnosis is uncertain and in differentiating bacterial from viral etiology. PCT substantially improved the ability of a clinical model including fever, cough, sputum production, abnormal chest auscultation, and dyspnea to discriminate pneumonia from other respiratory diseases in adults [44]. This same study also demonstrated that PCT had the highest diagnostic accuracy compared to CRP, leukocyte count, body temperature, chest auscultation, and sputum production in predicting radiographic infiltrate compared to noninfectious respiratory diagnoses [44]. Other studies have found that PCT can differentiate pneumonia from asthma exacerbation in adults with lower respiratory signs and symptoms. [27].

The lack of a sensitive etiologic gold standard in pneumonia makes evaluation of new etiologic tests challenging. Some of the strongest supporting evidence of the ability of PCT to differentiate bacterial from viral respiratory etiologies in adults stems from interventional studies that used PCT to guide the use of antibiotic therapy [45•]. These trials compared the provision of guidance around antibiotic use depending on the PCT with standard care at the discretion of the treating clinician (Table 2) [42, 46–48]. The primary outcomes were clinical outcomes, assuming that if a patient recovered without antibiotics, there was no serious bacterial illness. A multicenter noninferiority trial of 1359 adults found that rates of overall adverse outcomes were similar between those in the PCT-guidance group compared to controls (15.4 vs. 18.9 %, difference −3.5 %, 95 % CI −7.6 to 0.4 %). The mean duration of antibiotic exposure (5.7 vs. 8.7 days) and antibiotic-associated adverse effects (19.5 vs. 28.1 %) were less frequent in the PCT-guidance group compared with controls [48].

Procalcitonin has also been shown to be associated with certain prognostic outcomes in adult CAP, including disease severity and mortality [49]. PCT has generally been found to be a stronger predictor of these outcomes than CRP or leukocyte count [44]. Serial measurements of PCT over time may more accurately describe outcomes, with persistently elevated PCT levels associated with worse outcomes and a declining level suggesting a promising outcome [50, 51]. Although these associations exist, there are dangers in relying on a single measurement of PCT to definitely rule out bacterial infection or predict prognosis. For example, PCT is not a marker of early infection, with typical increases occurring approximately 6 h after stimulation [52]. Other markers, such as proadrenomedullin (see below), are likely better prognostic markers when measured in isolation at presentation; however, further study is required to fully evaluate the role of proadrenomedullin in prognosis compared to PCT.

Pediatric Studies

Procalcitonin has been studied as a marker of serious bacterial infection (SBI) in children in several contexts, including the febrile neonate [53•], fever without focus in children younger than 3 years [54, 55], urinary tract infections [56], sickle cell disease [57], and in those with central venous catheters [58].

Studies examining the use of PCT to differentiate viral from bacterial etiology in childhood CAP demonstrate conflicting results. Several studies report that PCT is better than CRP in distinguishing viral from bacterial CAP [20, 59, 60], yet several others report that PCT was of no use in this distinction [13, 61–63]. These differences are a reflection of heterogeneous methods, in addition to the challenges in detecting etiology in children with CAP. A recent study attempted to circumvent this challenge by obtaining polymerase chain reaction tests for viruses and pneumococcus, in addition to acute and convalescent pneumococcal serology and standard blood and nasal cultures, to identify pneumococcal pneumonia. This study found that a PCT value ≤0.5 ng/mL ruled out pneumococcal CAP in >90 % of cases (negative likelihood ratio 0.08), while a PCT ≥1.5 ng/mL in combination with a positive pneumococcal urinary antigen had a diagnostic probability for pneumococcal pneumonia of almost 80 % (positive likelihood ratio 4.59) [64•]. Another study found that PCT ≥2 ng/mL had a negative predictive value of 95 % (95% CI 89–100 %) for differentiating bacteremic pneumonia from viral infection in children [65]. Again, these results need to be interpreted with caution and replicated given the challenges of defining CAP etiology.

Two studies have attempted to extrapolate the adult PCT-guided antibiotic therapy algorithm for use in children. In one, the PCT-guided group received fewer antibiotic prescriptions, had shorter antibiotic duration, and experienced few antibiotic-related adverse events [66], while the other found

Table 2 Recommendations for initiation of antibiotics in adults with community-acquired pneumonia in the emergency department using procalcitonin

Procalcitonin (PCT) value (mcg/L)	Antibiotic initiation recommendation	Comments
<0.10	Strongly discouraged	If no clinical improvement, recheck PCT in 6–12 h
0.10–0.24	Discouraged	
0.25–0.5	Encouraged	Recheck PCT every 2–3 days to assist in deciding to discontinue antibiotics
>0.5	Strongly encouraged	

Adapted from Schuetz P et al. *Arch Intern Med* 2011

no difference in antibiotic prescribing rates, antibiotic side effects, or safety measures, but the duration of antibiotic therapy was shorter in the PCT-guided group [67•]. These studies are limited in their generalizability and sample size, and future research must clarify if PCT has a role in guiding antibiotic therapy in children [45•].

Procalcitonin has been found to be a marker of disease severity in children with CAP; this data is not of high quality, and further studies are necessary to define the role of PCT in evaluating and predicting disease severity. One study of 100 children with CAP (26 hospitalized, 74 outpatients) found PCT to be related to disease severity, as defined by the need for hospitalization and alveolar infiltrates, but not etiology [63]. Unfortunately, this study did not examine additional more clinically relevant and less subjective markers of severity.

Although initial studies are promising, research using high-quality, rigorous methodology needs to further define the role of PCT in diagnosis and risk stratification for pediatric CAP. It is likely that a combination of clinical factors and biomarkers, including PCT, will be of most use for diagnosis and prognosis of childhood CAP.

Proadrenomedullin

Adrenomedullin is produced at times of physiologic stress and has vasodilatory, antimicrobial, and anti-inflammatory properties. Levels of adrenomedullin have been shown to increase with disease severity in adults with sepsis [68]. Serum levels of adrenomedullin are difficult to measure due to rapid clearance from the circulation [69]. The midregional fragment of proadrenomedullin is more stable, easier to measure, and directly reflects levels of adrenomedullin [70]. When compared with CRP and leukocyte count in adults with CAP, proadrenomedullin increased with escalating disease severity [71]. Studies of proadrenomedullin in adult CAP have found that proadrenomedullin independently predicted mortality and adverse outcomes with similar accuracy of clinical risk scores, such as the Pneumonia Severity Index. However, when proadrenomedullin was added to the clinical severity scores, it enhanced severity prediction compared with the score alone and was more consistently accurate in predicting prognosis than other blood biomarkers [71, 72••, 73–75]. In addition, proadrenomedullin was found to have high short- and long-term prognostic accuracy [74]. There has only been one small study of hospitalized children with CAP that found that proadrenomedullin levels were associated with the development of pneumonia-associated complications [76]. In summary, proadrenomedullin appears to be a promising biomarker, particularly around prognosis, in adult CAP. Further research is required to understand if proadrenomedullin affects clinical decision-making and predicts patient outcomes and to determine if there is a role for proadrenomedullin in the management of children with CAP.

Summary

The PIDS/IDSA pediatric pneumonia guideline strongly recommends that acute phase reactants, including CRP and PCT, should not be used as the sole determinant to distinguish between viral and bacterial etiology and should not be routinely measured in fully immunized children who are managed as outpatients (Table 1). The pediatric guideline is less committed in patients with more severe disease, stating that they may be of use in patients with more serious disease to guide clinical management and assess response to treatment [4••]. The adult ATS/IDSA pneumonia guidelines do not provide any recommendations regarding the use of CRP or other acute phase reactants in the diagnosis and management of adult CAP (Table 1). Other biomarkers, including cytokines, copeptin, cortisol, d-dimer, and brain natriuretic peptide, have been examined in CAP, but there is not sufficient data to recommend any of these markers in clinical practice. Based on current and emerging data, PCT or proadrenomedullin may be used in combination with clinical features to assist in management decisions for CAP in the future.

Biomarkers of Pathogen Activity

Blood, Sputum, and Pleural Fluid Cultures

Conventional microbiological techniques, such as cultures from sterile sites including blood or pleural fluid, demonstrate high specificity and are commonly used as diagnostic tools for

patients with CAP. The sensitivity and specificity of cultures increase when the sample has been obtained 24 h prior to the first dose of antibiotics administered [77]. The quality of the sample is also critically important when collecting respiratory secretion samples such as sputum for culture [78]. Among 105 adult patients with blood culture-confirmed pneumococcal pneumonia, sputum cultures had a sensitivity of 79 % and increased to 86 % when excluding patients who received antibiotics within 24 h of obtaining the sputum sample. Although the majority of adults can produce a sputum specimen for microbiologic analysis, children have difficulty producing sufficient sputum of adequate quality for culture and young children are more likely to swallow the sputum than expectorate it [79]. In addition, up to two-thirds of children under 5 years presenting with CAP symptoms are colonized with common bacterial causes of pneumonia, such as *Streptococcus pneumoniae*, compared with only 6–14 % of adults. Therefore, sputum specimens from children are typically contaminated with colonizing bacteria [80, 81].

Blood cultures obtained in children are typically positive in less than 7 % of cases; therefore, in the majority of cases, when the blood cultures are negative, it can be unclear how to proceed with antibiotic prescribing [82•]. The main limitations of any culture technique are false-negative cultures, false-positive cultures due to contamination, and the amount of time to return a positive result (approximately 1–5 days). Blood cultures are recommended for both adults and children who are hospitalized with CAP, in addition to those with specific indications. Sputum cultures are recommended from adults with specific indications and from children hospitalized with CAP who are developmentally able to produce an adequate sputum sample. As cultures from pleural fluid are more sensitive and specific than blood cultures, it is recommended that pleural fluid culture should be performed whenever pleural fluid is obtained (Table 1) [3••, 4••].

Nucleic Acid Detection Tests

As blood cultures for *S. pneumoniae* are rarely positive in CAP, alternative methods of organism detection have been developed. Nucleic acid tests (NAT) most commonly use polymerase chain reaction (PCR) methodology. PCR has many benefits compared with culture-based techniques: it is not influenced substantially by prior antibiotic therapy, it can be performed for multiple respiratory pathogens, it can indicate antibiotic-resistant genes, and, most importantly, results can be used for timely clinical management [83]. For *S. pneumoniae*, known pneumococcal surface antigens such as pneumococcal autolysin A (lytA), pneumococcal surface adhesin A (psaA), gene fragment Spn9802, and a pneumococcus-produced toxin, pneumolysin (ply), have all been evaluated using PCR techniques with variable sensitivity and specificity when compared with blood and sputum culture [83–89]. Compared with blood cultures, results from lytA PCR on average have the highest sensitivity and specificity compared to the other gene fragments [83]. In addition, multiplex PCR for psaA, lytA, and ply simultaneously showed no additional improvement in pneumococcal detection over performing the PCR for each gene fragment separately [83]. Due to the process of gene amplification in PCR, it is possible that false-positives could occur because of amplifying the viridians group of streptococcus-related sequences or detection of dead bacteria post-infection. Children who are healthy may also have false-positive PCR results due to colonization with pneumococcus.

PCR testing can be extremely helpful in determining other prevalent organisms in children, such as *M. pneumoniae* and influenza A and B, thereby guiding and determining the need for antimicrobial therapy. Although the PIDS/IDSA guideline recommends PCR testing in children for *M. pneumoniae*, it is unclear from the literature the best specimen type to use (e.g., nasopharyngeal swabs, sputum) or the best set of PCR primers [4••]. Therefore, it is recommended that clinicians familiarize themselves with the performance characteristics of their locally available test for *M. pneumoniae* when applicable [4••]. The PIDS/IDSA guideline also recommends that influenza A and B PCR testing (or rapid influenza antigen testing) from nasal specimens and PCR testing from pleural fluid samples for *Staphylococcus aureus* and *S. pneumoniae* be performed. Viruses account for greater than half of all pneumonias in children, with roughly 20 % being viral-bacterial coinfections [90]. PCR testing for other viruses (e.g., respiratory syncytial virus) in children may be helpful to minimize unnecessary antibiotic use when a bacterial coinfection is not suspected (Table 1) [4••].

Although evidence that bacterial burden in blood is a predictor of severity has existed for decades, its utility was limited by burdensome and time-consuming culture techniques. Newer quantitative real-time PCR allows such quantification to occur quickly and with substantially less effort than conventional culture-based techniques. Studies in adults with CAP have found a strong correlation with high pneumococcal bacterial loads and increased risk of prolonged hospital length of stay, ICU admission, higher severity scores, systemic inflammatory response syndrome, septic shock, and mortality, with a threshold effect (i.e., there is a certain number of organisms above which these adverse events occur) [91]. To date, there has been no substantial study that investigates the role of pneumococcal bacterial load in children with CAP.

Urine Antigen Test

Antigen tests can be performed on urine, CSF, and blood. The most commonly used are urinary antigen tests which have been developed and validated for selected bacterial pathogens, namely *S. pneumoniae* and *Legionella pneumophila* [92]. The advantages of these tests are the ease of performing the test

and the noninvasive nature of sample collection. For pneumococcal pneumonia, the urine immunochromatographic test detects c-polysaccharide found on the cell wall [84]. For adults, urinary antigen tests for pneumococcus have been shown to have a sensitivity of 60–82 % and a specificity of 92–97 % [92–94]. For *L. pneumophila*, the urinary antigen test only detects serogroup 1 but has a sensitivity of 70–90 % and a specificity of >99 % [95]. In children, sensitivity and specificity of pneumococcal urine antigen test when compared with blood culture are 96–100 and 62–92 %, respectively [94, 96, 97]. Up to two-thirds of children under 5 years are also colonized with common bacterial causes of pneumonia, such as *S. pneumoniae*, compared with only 6–14 % of adults, therefore making urinary antigen tests difficult to interpret in children [81]. Urine antigen tests are recommended for detecting pathogens to guide antibiotic treatment in adult patients; however, due to the high rate of bacterial colonization, urine antigen tests are not recommended in children [3••, 4••].

Emerging Biomarkers

A systems biology approach to diagnostic testing has emerged with the identification of genes, proteins, and metabolites that represent the interaction between pathogen and host. This approach focused on pathogen-specific host responses represents a potential paradigm shift in pneumonia diagnostics. Initial studies have demonstrated that gene expression profiles of peripheral blood leukocytes in patients with lower respiratory tract infection can accurately distinguish influenza viral infection from bacterial infection, in addition to predicting disease severity [98•, 99]. Metabolomic studies, the study of metabolites, have distinguished different etiologies of CAP in urine samples in both adults and children; however, these studies are limited by small sample sizes [100•, 101]. The benefits of a metabolomic study are the relatively quick processing time of samples (e.g., a few hours) compared to traditional microbiological techniques (e.g., a few days). A substantial limitation of the systems biology approach is the expertise required to analyze the complex data produced.

Conclusion

Biomarkers offer distinct advantages in the diagnosis and management of CAP, often acting as important adjuncts to a well-performed history and physical examination. Commonly used biomarkers, such as leukocyte count, have been found to lack diagnostic accuracy; however, newer biomarkers such as procalcitonin and proadrenomedullin are emerging as promising alternative measures of the host response to infection in CAP. These biomarkers show potential as diagnostic, therapeutic, and prognostic indicators in both adult and pediatric CAP, yet further research is required to clearly understand the role of these biomarkers in clinical practice.

Blood culture is still the most common pathogen detection technique used in CAP due its widespread availability and relatively low cost. Its use in targeting antibiotic therapy in the management of pneumonia continues to be limited by the large potential for false-negative results and a turnaround time of days, rather than hours, for results. Newer quantitative real-time PCR techniques are specific to the organism and not widely available for clinical use; however, they are emerging as a promising method of pathogen detection.

Compliance with Ethics Guidelines

Conflict of Interest Lilliam Ambroggio and Todd Florin have no disclosures relevant to this work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Zhou F, Kyaw MH, Shefer A, Winston CA, Nuorti JP. Health care utilization for pneumonia in young children after routine pneumococcal conjugate vaccine use in the United States. Arch Pediatr Adolesc Med. 2007;161:1162–8.
2. Lode HM. Managing community-acquired pneumonia: a European perspective. Respir Med. 2007;101:1864–73.
3.•• Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis Off Publ Inf Dis Soc Am. 2007;44 Suppl 2:S27–72. *Evidence-based consensus guidelines for the management of community-acquired pneumonia in adults*.
4.•• Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Inf Dis Off Publ Inf Dis Soc Am. 2011;53:e25–76. *Evidence-based consensus guidelines for the management of community-acquired pneumonia in children*.
5. Florin TA, French B, Zorc JJ, Alpern ER, Shah SS. Variation in emergency department diagnostic testing and disposition outcomes in pneumonia. Pediatrics. 2013;132:237–44.
6. Neuman MI, Shah SS, Shapiro DJ, Hersh AL. Emergency department management of childhood pneumonia in the United States prior to publication of national guidelines. Acad Emerg Med Off J Soc Acad Emerg Med. 2013;20:240–6.
7. Neuman MI, Graham D, Bachur R. Variation in the use of chest radiography for pneumonia in pediatric emergency departments. Pediatr Emerg Care. 2011;27:606–10.

8. Dedier J, Singer DE, Chang Y, Moore M, Atlas SJ. Processes of care, illness severity, and outcomes in the management of community-acquired pneumonia at academic hospitals. Arch Intern Med. 2001;161:2099–104.
9. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243–50.
10. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377–82.
11. Strimbu K, Tavel JA. What are biomarkers? Curr Opin HIV AIDS. 2010;5:463–6.
12. Schutzle H, Forster J, Superti-Furga A, Berner R. Is serum procalcitonin a reliable diagnostic marker in children with acute respiratory tract infections? A retrospective analysis. Eur J Pediatr. 2009;168:1117–24.
13. Toikka P, Irjala K, Juven T, et al. Serum procalcitonin, C-reactive protein and interleukin-6 for distinguishing bacterial and viral pneumonia in children. Pediatr Infect Dis J. 2000;19:598–602.
14. Lynch T, Bialy L, Kellner JD, et al. A systematic review on the diagnosis of pediatric bacterial pneumonia: when gold is bronze. PLoS One. 2010;5:e11989.
15. Van den Bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. BMJ. 2011;342:d3082.
16. Ballin A, Osadchy A, Klivitsky A, Dalal I, Lishner M. Age-related leukocyte and cytokine patterns in community-acquired bronchopneumonia. Isr Med Assoc J IMAJ. 2006;8:388–90.
17. Don M, Valent F, Korppi M, Canciani M. Differentiation of bacterial and viral community-acquired pneumonia in children. Pediatr Int Off J Jpn Pediatr Soc. 2009;51:91–6.
18. Elemraid MA, Rushton SP, Thomas MF, Spencer DA, Gennery AR, Clark JE. Utility of inflammatory markers in predicting the aetiology of pneumonia in children. Diagn Microbiol Infect Dis. 2014;79:458–62.
19. Hoshina T, Nanishi E, Kanno S, Nishio H, Kusuhara K, Hara T. The utility of biomarkers in differentiating bacterial from non-bacterial lower respiratory tract infection in hospitalized children: difference of the diagnostic performance between acute pneumonia and bronchitis. J Inf Chemother Off J Jpn Soc Chemother. 2014;20(10):616–20.
20. Moulin F, Raymond J, Lorrot M, et al. Procalcitonin in children admitted to hospital with community acquired pneumonia. Arch Dis Child. 2001;84:332–6.
21. Summah H, Qu JM. Biomarkers: a definite plus in pneumonia. Mediat Inflamm. 2009;2009:675753.
22. Virkki R, Juven T, Rikalainen H, Svedstrom E, Mertsola J, Ruuskanen O. Differentiation of bacterial and viral pneumonia in children. Thorax. 2002;57:438–41.
23. Pereira JM, Teixeira-Pinto A, Basilio C, Sousa-Dias C, Mergulhao P, Paiva JA. Can we predict pneumococcal bacteremia in patients with severe community-acquired pneumonia? J Crit Care. 2013;28:970–4.
24. Korppi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. Eur Respir J. 1997;10:1125–9.
25. Purcell K, Fergie J. Lack of usefulness of an abnormal white blood cell count for predicting a concurrent serious bacterial infection in infants and young children hospitalized with respiratory syncytial virus lower respiratory tract infection. Pediatr Infect Dis J. 2007;26:311–5.
26. Luna CM. C-reactive protein in pneumonia: let me try again. Chest. 2004;125:1192–5.
27. Bafadhel M, Clark TW, Reid C, et al. Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. Chest. 2011;139:1410–8.
28. Flood RG, Badik J, Aronoff SC. The utility of serum C-reactive protein in differentiating bacterial from nonbacterial pneumonia in children: a meta-analysis of 1230 children. Pediatr Infect Dis J. 2008;27:95–9.
29. Heiskanen-Kosma T, Korppi M. Serum C-reactive protein cannot differentiate bacterial and viral aetiology of community-acquired pneumonia in children in primary healthcare settings. Scand J Infect Dis. 2000;32:399–402.
30. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. Infection. 2000;28:68–73.
31. Smith RP, Lipworth BJ. C-reactive protein in simple community-acquired pneumonia. Chest. 1995;107:1028–31.
32. Zhydkov A, Christ-Crain M, Thomann R, et al. Utility of procalcitonin, C-reactive protein and white blood cells alone and in combination for the prediction of clinical outcomes in community-acquired pneumonia. Clin Chem Lab Med CCLM / FESCC 2014. doi:10.1515/cclm-2014-0456.
33. Hohenthal U, Hurme S, Helenius H, et al. Utility of C-reactive protein in assessing the disease severity and complications of community-acquired pneumonia. Clin Microbiol Infect. 2009;15:1026–32.
34. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. Am J Med. 2008;121:219–25.
35. Bruns AH, Oosterheert JJ, Hak E, Hoepelman AI. Usefulness of consecutive C-reactive protein measurements in follow-up of severe community-acquired pneumonia. Eur Respir J. 2008;32:726–32.
36. Coelho L, Povoa P, Almeida E, et al. Usefulness of C-reactive protein in monitoring the severe community-acquired pneumonia clinical course. Crit Care. 2007;11:R92.
37. Hirakata Y, Yanagihara K, Kurihara S, et al. Comparison of usefulness of plasma procalcitonin and C-reactive protein measurements for estimation of severity in adults with community-acquired pneumonia. Diagn Microbiol Infect Dis. 2008;61:170–4.
38. Brunkhorst FM, Al-Nawas B, Krummenauer F, Forycki ZF, Shah PM. Procalcitonin, C-reactive protein and APACHE II score for risk evaluation in patients with severe pneumonia. Clin Microbiol Infect. 2002;8:93–100.
39. Le Moullec JM, Jullienne A, Chenais J, et al. The complete sequence of human preprocalcitonin. FEBS Lett. 1984;167:93–7.
40. Becker KL, Nylen ES, White JC, Muller B, Snider Jr RH. Clinical review 167: procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab. 2004;89:1512–25.
41. Muller B, Becker KL, Schachinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med. 2000;28:977–83.
42. Christ-Crain M, Opal SM. Clinical review: the role of biomarkers in the diagnosis and management of community-acquired pneumonia. Crit Care. 2010;14:203.
43. Snider Jr RH, Nylen ES, Becker KL. Procalcitonin and its component peptides in systemic inflammation: immunochemical characterization. J Investig Med Off Publ Am Fed Clin Res. 1997;45:552–60.
44. Muller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis. 2007;7:10.
45.• Soni NJ, Samson DJ, Galaydick JL, Vats V, Pitrak DL, Aronson N. Procalcitonin-guided antibiotic therapy. Comparative effectiveness review no. 78. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based

Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 12(13)-EHC124-EF. Rockville: Agency for Healthcare Research and Quality; 2012. *A systematic review of 18 randomized trials demonstrating decreased antibiotic use in adult patients with community-acquired pneumonia when procalcitonin guidance is used.*

46. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet. 2004;363:600–7.
47. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med. 2006;174:84–93.
48. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA. 2009;302:1059–66.
49. Andrijevic I, Matijasevic J, Andrijevic L, Kovacevic T, Zaric B. Interleukin-6 and procalcitonin as biomarkers in mortality prediction of hospitalized patients with community acquired pneumonia. Ann Thorac Med. 2014;9:162–7.
50. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med. 2006;34:2596–602.
51. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med. 2001;164:396–402.
52. Gendrel D, Bohuon C. Procalcitonin as a marker of bacterial infection. Pediatr Infect Dis J. 2000;19:679–87.
53.• Gomez B, Bressan S, Mintegi S, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. Pediatrics. 2012;130:815–22. *This retrospective study of 1112 well-appearing febrile infants <3 months of age with fever without source demonstrated that procalcitonin performs better than C-reactive protein in identifying infants with invasive bacterial infections and was the best marker to rule out invasive bacterial infection*.
54. Yo CH, Hsieh PS, Lee SH, et al. Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without source: a systematic review and meta-analysis. Ann Emerg Med. 2012;60:591–600.
55. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. Pediatr Infect Dis J. 2007;26:672–7.
56. Leroy S, Fernandez-Lopez A, Nikfar R, et al. Association of procalcitonin with acute pyelonephritis and renal scars in pediatric UTI. Pediatrics. 2013;131:870–9.
57. Unal S, Arslankoylu AE, Kuyucu N, Aslan G, Erdogan S. Procalcitonin is more useful than C-reactive protein in differentiation of fever in patients with sickle cell disease. J Pediatr Hematol Oncol. 2012;34:85–9.
58. Kasem AJ, Bulloch B, Henry M, Shah K, Dalton H. Procalcitonin as a marker of bacteremia in children with fever and a central venous catheter presenting to the emergency department. Pediatr Emerg Care. 2012;28:1017–21.
59. Prat C, Dominguez J, Rodrigo C, et al. Procalcitonin, C-reactive protein and leukocyte count in children with lower respiratory tract infection. Pediatr Infect Dis J. 2003;22:963–8.
60. Hatzistilianou M, Hitoglou S, Gougoustamou D, et al. Serum procalcitonin, adenosine deaminase and its isoenzymes in the aetiological diagnosis of pneumonia in children. Int J Immunopathol Pharmacol. 2002;15:119–27.
61. Korppi M, Remes S, Heiskanen-Kosma T. Serum procalcitonin concentrations in bacterial pneumonia in children: a negative result in primary healthcare settings. Pediatr Pulmonol. 2003;35:56–61.
62. Korppi M, Remes S. Serum procalcitonin in pneumococcal pneumonia in children. Eur Respir J. 2001;17:623–7.
63. Don M, Korppi M, Valent F, Vainionpaa R, Canciani M. Human metapneumovirus pneumonia in children: results of an Italian study and mini-review. Scand J Infect Dis. 2008;40:821–6.
64.• Galetto-Lacour A, Alcoba G, Posfay-Barbe KM, et al. Elevated inflammatory markers combined with positive pneumococcal urinary antigen are a good predictor of pneumococcal community-acquired pneumonia in children. Pediatr Infect Dis J. 2013;32:1175–9. *This prospective study of pneumonia biomarkers in 75 children included one of the most comprehensive sets of etiology markers, including antibodies against 5 pneumococcal surface proteins, viral serologies, nasopharyngeal cultures and polymerase chain reaction for 13 respiratory viruses, blood pneumococcal PCR, pneumococcal urinary antigen, procalcitonin and C-reactive protein. The study found that PCT and CRP are reliable predictors of pneumococcal pneumonia, and the combination of elevated PCT or CRP with a positive urinary antigen test is a strong predictor of pneumococcal pneumonia*.
65. Nascimento-Carvalho CM, Cardoso MR, Barral A, et al. Seasonal patterns of viral and bacterial infections among children hospitalized with community-acquired pneumonia in a tropical region. Scand J Infect Dis. 2010;42:839–44.
66. Esposito S, Tagliabue C, Picciolli I, et al. Procalcitonin measurements for guiding antibiotic treatment in pediatric pneumonia. Respir Med. 2011;105:1939–45.
67.• Baer G, Baumann P, Buettcher M, et al. Procalcitonin Guidance to Reduce Antibiotic Treatment of Lower Respiratory Tract Infection in Children and Adolescents (ProPAED): a randomized controlled trial. PLoS One. 2013;8:e68419. *The randomized study examined use of procalcitonin guidance in children and found that procalcitonin guidance reduced antibiotic exposure with no difference in impairment of daily activities*.
68. Hirata Y, Mitaka C, Sato K, et al. Increased circulating adrenomedullin, a novel vasodilatory peptide, in sepsis. J Clin Endocrinol Metab. 1996;81:1449–53.
69. Eto T. A review of the biological properties and clinical implications of adrenomedullin and proadrenomedullin N-terminal 20 peptide (PAMP), hypotensive and vasodilating peptides. Peptides. 2001;22:1693–711.
70. Struck J, Tao C, Morgenthaler NG, Bergmann A. Identification of an adrenomedullin precursor fragment in plasma of sepsis patients. Peptides. 2004;25:1369–72.
71. Christ-Crain M, Morgenthaler NG, Stolz D, et al. Pro-adrenomedullin to predict severity and outcome in community-acquired pneumonia [ISRCTN04176397]. Crit Care. 2006;10:R96.
72.•• Albrich WC, Dusemund F, Ruegger K, et al. Enhancement of CURB65 score with proadrenomedullin (CURB65-A) for outcome prediction in lower respiratory tract infections: derivation of a clinical algorithm. BMC Inf Dis. 2011;11:112. *This study derived a new clinical algorithm that combines the CURB-65 score, an established clinical severity score for adults with CAP, with proadrenomedullin to produce the CURB65-A score. This new score provided better prediction of death and adverse events than the CURB65 score*.
73. Huang DT, Angus DC, Kellum JA, et al. Midregional proadrenomedullin as a prognostic tool in community-acquired pneumonia. Chest. 2009;136:823–31.
74. Bello S, Lasierra AB, Minchole E, et al. Prognostic power of proadrenomedullin in community-acquired pneumonia is independent of aetiology. Eur Respir J. 2012;39:1144–55.

75. Renaud B, Schuetz P, Claessens YE, Labarere J, Albrich W, Mueller B. Proadrenomedullin improves Risk of Early Admission to ICU score for predicting early severe community-acquired pneumonia. Chest. 2012;142:1447–54.
76. Sarda Sanchez M, Hernandez JC, Hernandez-Bou S, Teruel GC, Rodriguez JV, Cubells CL. Pro-adrenomedullin usefulness in the management of children with community-acquired pneumonia, a preliminar prospective observational study. BMC Res Notes. 2012;5:363.
77. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. Clin Infect Dis. 2004;39:165–9.
78. Murdoch DR, O'Brien KL, Driscoll AJ, et al. Laboratory methods for determining pneumonia etiology in children. Clin Infect Dis. 2012;54 Suppl 2:S146–52.
79. Laing R, Slater W, Coles C, et al. Community-acquired pneumonia in Christchurch and Waikato 1999–2000: microbiology and epidemiology. N Z Med J. 2001;114:488–92.
80. Millar EV, Watt JP, Bronsdon MA, et al. Indirect effect of 7-valent pneumococcal conjugate vaccine on pneumococcal colonization among unvaccinated household members. Clin Infect Dis. 2008;47:989–96.
81. Abdullahi O, Nyiro J, Lewa P, Slack M, Scott JA. The descriptive epidemiology of Streptococcus pneumoniae and Haemophilus influenzae nasopharyngeal carriage in children and adults in Kilifi district, Kenya. Pediatr Infect Dis J. 2008;27:59–64.
82.• Myers AL, Hall M, Williams DJ, et al. Prevalence of bacteremia in hospitalized pediatric patients with community-acquired pneumonia. Pediatr Infect Dis J. 2013;32:736–40. *This multicenter retrospective study of 658 children with CAP found a bacteremia prevalence rate of 7%, with blood culture results changing antibiotic management in 26-65% of patients. The study concluded that blood cultures are useful in hospitalized children with CAP and should prompt a change to narrow-spectrum antibiotic therapy if positive with sensitive organisms.*
83. Carvalho Mda G, Tondella ML, McCaustland K, et al. Evaluation and improvement of real-time PCR assays targeting lytA, ply, and psaA genes for detection of pneumococcal DNA. J Clin Microbiol. 2007;45:2460–6.
84. Song JY, Eun BW, Nahm MH. Diagnosis of pneumococcal pneumonia: current pitfalls and the way forward. Infect Chemother. 2013;45:351–66.
85. Butler JC, Bosshardt SC, Phelan M, et al. Classical and latent class analysis evaluation of sputum polymerase chain reaction and urine antigen testing for diagnosis of pneumococcal pneumonia in adults. J Inf Dis. 2003;187:1416–23.
86. Michelow IC, Lozano J, Olsen K, et al. Diagnosis of Streptococcus pneumoniae lower respiratory infection in hospitalized children by culture, polymerase chain reaction, serological testing, and urinary antigen detection. Clin Inf Dis Off Publ Inf Dis Soc Am. 2002;34:E1–11.
87. Stralin K, Tornqvist E, Kaltoft MS, Olcen P, Holmberg H. Etiologic diagnosis of adult bacterial pneumonia by culture and PCR applied to respiratory tract samples. J Clin Microbiol. 2006;44:643–5.
88. Abdeldaim G, Herrmann B, Molling P, et al. Usefulness of real-time PCR for lytA, ply, and Spn9802 on plasma samples for the diagnosis of pneumococcal pneumonia. Clin Microbiol Inf Off Publ Eur Soc Clin Microbiol Inf Dis. 2010;16:1135–41.
89. Azzari C, Cortimiglia M, Moriondo M, et al. Pneumococcal DNA is not detectable in the blood of healthy carrier children by real-time PCR targeting the lytA gene. J Med Microbiol. 2011;60:710–4.
90. Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics. 2004;113:701–7.
91. Rello J, Lisboa T, Lujan M, et al. Severity of pneumococcal pneumonia associated with genomic bacterial load. Chest. 2009;136:832–40.
92. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis. 2011;52 Suppl 4:S296–304.
93. Smith MD, Derrington P, Evans R, et al. Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW Streptococcus pneumoniae urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol. 2003;41:2810–3.
94. Tzeng DH, Lee YL, Lin YH, Tsai CA, Shi ZY. Diagnostic value of the Binax NOW assay for identifying a pneumococcal etiology in patients with respiratory tract infection. J Microbiol Immunol Infect. 2006;39(1):39–44.
95. Murdoch DR. Diagnosis of Legionella infection. Clin Infect Dis. 2003;36:64–9.
96. Neuman MI, Harper MB. Evaluation of a rapid urine antigen assay for the detection of invasive pneumococcal disease in children. Pediatrics. 2003;112:1279–82.
97. Stralin K, Holmberg H. Usefulness of the Streptococcus pneumoniae urinary antigen test in the treatment of community-acquired pneumonia. Clin Infect Dis. 2005;41:1209–10.
98.• Ramilo O, Allman W, Chung W, et al. Gene expression patterns in blood leukocytes discriminate patients with acute infections. Blood. 2007;109:2066–77. *This study used RNA microarray technology on peripheral blood leukocytes to discover gene expression patterns able to discriminate patients with influenza A infection from those with S. pneumoniae infection, suggesting a paradigm shift in etiologic diagnosis in pneumonia.*
99. Mejias A, Dimo B, Suarez NM, et al. Whole blood gene expression profiles to assess pathogenesis and disease severity in infants with respiratory syncytial virus infection. PLoS Med. 2013;10:e1001549.
100.• Slupsky CM, Rankin KN, Fu H, et al. Pneumococcal pneumonia: potential for diagnosis through a urinary metabolic profile. J Proteome Res. 2009;8:5550–8. *This study found that the urinary metabolite profile for pneumococcal pneumonia was significantly different from profiles for viral and other bacterial forms of pneumonia. This suggests that an easily obtainable, noninvasive specimen such as urine may be used to predict etiology and guide antibiotic therapy in CAP.*
101. Laiakis EC, Morris GA, Fornace AJ, Howie SR. Metabolomic analysis in severe childhood pneumonia in the Gambia, West Africa: findings from a pilot study. PLoS One 2010;5.