Diagnosing Viral and Atypical Pathogens in the Setting of Community-Acquired Pneumonia

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KEYWORDS

• Pneumonia • Viral • Diagnostic • Point of care

KEY POINTS

- The concept of atypical pneumonia is outdated because clinically it is impossible to determine the pathogen.
- Nucleic acid detection is now the standard diagnostic method for all these pathogens, having replaced older serologic and antigen detection methods.
- Multiple pathogens are commonly detected in patients, particularly with *Legionella*, *Mycoplasma*, and *Chlamydia*.

INTRODUCTION

Despite many promises that molecular diagnostics would transform the management of infection, empiric therapy remains the standard of care in community-acquired pneumonia (CAP). Outside of etiologic studies, the vast majority of patients never have a pathogen diagnosed as the cause of their pneumonia. Although physicians are generally quite comfortable with empiric therapy, the need to guess and fear of missing an important pathogen inevitably leads to a broader than necessary spectrum of coverage, particularly in the setting of more severe illness.

That viruses are an important cause of pneumonia has been known since the identification of influenza in the early 1930s.[1] Despite an awareness that viruses can cause CAP, it is only recently that they have appeared as more than a footnote on the list of common pathogens. However, with modern generations of diagnostic panels, and particularly nucleic acid amplification tests, viral pathogens are being identified increasingly as not only common causes of CAP, but possibly as being overall more common that bacteria.[2,3] With more sensitive tests has also come confirmation that patients with CAP frequently have multiple pathogens present, particularly the combination of bacterial and viral infection.

The term "atypical pneumonia" was coined in first half of the 20th century and used to describe pneumonia owing to pathogens that were not detectable by standard Gram staining or traditional culture methods and typically associated with headache, low-grade fever, cough, and malaise. The predominant pathogens that have become associated with atypical pneumonia are *Mycoplasma pneumoniae* (first identified in human lung in 1944),[4] *Legionella pneumophila* (first identified as a significant pneumonia pathogen in 1977 after the outbreak at a convention in Philadelphia in 1976)[5] and *Chlamydophila pneumoniae* (first identified in the respiratory tract

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in 1984).[6] A variety of different species of these genera are now recognized as pneumonia pathogens.

This review covers the main approaches to the diagnosis of atypical and viral infections in the setting of pneumonia. The most common approach has been the use of pathogen-specific assays for use in urine, blood, or sputum. Although serologic tests based on detecting antibodies to specific pathogens were the predominant technique for decades, they all have limitations in early disease before an adaptive immune response being constituted as well as issues of cross-reactivity reducing specificity. Polymerase chain reaction (PCR)–based techniques are now the primary modality for the detection of atypical pathogens in most settings. More recently, there has been the development of multipathogen detection platforms that have become used increasingly in the setting of pneumonia.

CLINICAL DIAGNOSIS

Before moving to laboratory tests, it is worth briefly looking at the evidence of whether there are any specific clinical or radiological features in CAP that help to deduce reliably the pathogen. There are definitely clinical features that are seen more commonly in some of the atypical pathogens than with disease owing to *Streptococcus pneumoniae*. Examples include erythema multiforme with *M pneumoniae*, diarrhea with *L pneumophila*, and rhinorrhea with influenza. However, there is ample evidence that no set of clinical symptoms or signs has sufficient predictive ability to rule in or out any atypical or viral pathogens, especially *M pneumoniae*[7] and *Legionella*.[8–10]

A number of nonmicrobiological tests have also been proposed as being able to discriminate between "atypical" and "typical" pathogens, including the peripheral white cell count and procalcitonin. Although peripheral white cell counts do tend to be lower in viral infections compared with bacterial infections, this is not particularly discriminating at an individual patient level and certainly not accurate enough to use to determine empiric therapy.[11] Procalcitonin seems to be more accurate than white cell count,[11] but does not discriminate between atypical bacterial infection and viral infection[12] and may be misleading, particularly in critically ill patients or in patients with bacterial and viral coinfection.[13] A definitive diagnosis based on detecting the infection pathogen(s), therefore, remains critical if we are to improve the accuracy of empiric therapy.

PATHOGEN-SPECIFIC APPROACHES

Legionella

Very little has changed in the diagnosis of *Legionella* infection since we reviewed this topic comprehensively 15 years ago.[14] In most settings, *Legionella* is underdiagnosed and therefore underrecognized owing to routine testing not being performed.[15] *Legionella* infections seem to be increasing in the United States,[16,17] possibly owing to recent climate change, including a number of severe outbreaks with multiple fatalities,[18] which has led to increased interest in its diagnosis.

Because *Legionellae* will not grow on standard culture media, the diagnosis has traditionally rested on either positive serology or a positive urinary antigen test. Both of these tests have significant limitations. In the case of serology, 20% or more of patients with culture-proven *Legionella* infection do not ever seroconvert,[19,20] and seroconversion may take months, requiring testing out to at least 2 months if not longer.[21] Urinary antigen testing is quite specific, but will only reliably detection *L pneumophila* serogroup 1, and usually serogroup 6, but in many areas other species (particularly *Legionella longbeachae* and *Legionella micdadei*) are more predominant. Despite these limitations, urinary antigen testing for *Legionella* is recommended in all patients with severe CAP (ie, admitted to the intensive care unit) for both diagnostic and public health reasons.[22]

The mainstay of diagnosis of *Legionella* infection has been from one or more of direct antigen detection or nucleic acid detection in respiratory secretions. Direct fluorescent antigen detection was developed in the pre-PCR era but have now largely been replaced by PCR because the latter is more sensitive, less technician dependent, and easier to automate. PCR tests for *Legionella* are a mix of "home-grown" assays and commercially available products, with reported sensitivity and specificity (using all other tests as the gold standard) in the range of 91% to 99% and 94% to 99%, respectively.[23] Because PCR tests for *Legionella* are generally able to detect all species,[24] not surprisingly they have a greater degree of sensitivity than urinary antigen testing.[23,25] There is, however, a reasonable argument for performing both urinary antigen testing and PCR on respiratory secretions because there is an increased diagnostic yield from this approach.[26] It is worth noting that both nasopharyngeal aspirates[27–29] and throat swabs[15] have substantially lower yields for the detection of *Legionella* by PCR, but may be of use in patients in whom it is not possible to get spontaneous or induced sputum samples.