Viruses and Lower Respiratory Tract Infections: Does More Mean Worse?

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The great Nobel laureate, Sir Peter Medawar (1915–1987), defined a virus as ‘a piece of bad news wrapped up in protein’. Although viruses are well recognized as causes of human lower respiratory tract infections (LRTI), determining the pathogenic role of individual viruses for a given patient is challenging, in part because the various laboratory methods used to document specific viruses in clinical specimens have considerable technical limitations that can affect the interpretation of results. No perfect ‘gold standard’ for laboratory viral diagnosis exists, and while this may not have mattered so much in the past, when so few treatment options were available for respiratory viral infections, we are now living in an era in which novel antiviral interventions are rapidly making their way toward being implemented into practice and the accurate documentation of viral infections in various patient settings is becoming increasingly important.

There are 2 main conceptual approaches to laboratory viral diagnosis: (1) testing for direct evidence of virus in clinical specimens from the site of infection, e.g. culture for replicating virus, electron microscopy for assembled virus, immunostaining for viral antigens, or molecular biology-based methods to detect viral nucleic acid; (2) testing for evidence of a host response to virus, in which serology, which measures the production of host antibody against virus in peripheral blood, is arguably the best-known and most commonly used technique. In this

issue of *Respiration*, Gencay et al. [1] used serology for a panel of 8 common human viruses (adenovirus, enterovirus, influenza viruses A and B, parainfluenza viruses 1, 2 and 3, and respiratory syncytial virus) to document evidence of acute viral infection in patients diagnosed with LRTI. Major endpoints studied included: comparison of the proportion of individuals showing positive viral serology between LRTI patients and healthy control subjects; associations of specific viruses with different clinical variants of LRTI (community-acquired pneumonia vs. acute bronchitis vs. acute exacerbation of chronic obstructive pulmonary disease); and whether viruses were associated with concomitant bacterial infections. The results showed evidence of viral infection in >80% of LRTI patients (approximately 30% of these patients had evidence of simultaneous infections) compared with approximately 20% of healthy control subjects who had serological evidence of viral infection, and for whom no instances of multiple viruses were documented. Adenovirus and respiratory syncytial virus were more commonly associated with community-acquired pneumonia than other forms of LRTI. Furthermore, 14/15 (93%) of LRTI patients with documented bacterial infection also had serological evidence of viral infection, consistent with the paradigm that acute viral infections can predispose to secondary bacterial infections of the respiratory tract.

Although the results implicate acute viral infections in a large majority of adults diagnosed with LRTI, the serology method used in this study had a number of limitations. For example, results were reported as 'positive' or 'negative', such that the relationship between the extent of change of antibody titer and clinical phenotype was not determined. In particular, a more quantitative approach might have provided more insights into the significance of positive viral serology documented in a proportion of healthy subjects. In addition, the serology panel did not test for various viruses that cause human respiratory tract infections (including LRTI), such as rhinovirus, metapneumovirus or coronaviruses, and it is unknown whether other pathogens could also have contributed to the clinical phenotype. Concerning rhinovirus, the large number (>100) of serotypes makes laboratory testing exceedingly difficult and, as the authors comment, some antigenic overlap exists between rhinovirus and enterovirus which could have affected interpretations of enterovirus serology results. It is now well established that before the advent of polymerase chain reaction (PCR) protocols, the role of rhinovirus in human respiratory tract infections was profoundly underappreciated, and in the current study, it is conceivable that the use of serology for viral diagnosis may have underestimated the impact of rhinovirus in the individuals studied.

The results also showed that a sizeable proportion of LRTI patients had positive serology for multiple viruses. Simultaneous infections of the human respiratory tract are being increasingly appreciated but their importance

for pathogenesis remains unresolved. For example, in pediatric populations, we and others have applied PCR-based panels for the detection of virus-specific nucleic acid in nasal specimens and have shown that simultaneous infections occur frequently [2, 3]; however, in neither study was a definitive relationship between the number of viruses detected and severity of clinical respiratory illness established. Moreover, in adults, it has been known for over a decade that virus-specific nucleic acid can often be detected by PCR in human lower airway secretions [4] and in lung tissue specimens [5], in contradistinction to the paradigm that the human lung is a sterile environment in health, but without an obvious relationship between number and type of viruses and clinical diagnosis. Part of the reason for this uncertainty may be related to the use of dichotomous outputs ('positive' vs. 'negative') for viral documentation. Future studies designed to quantify viral load may shed new light on the relative contributions of specific viruses to the clinical phenotype in the setting of simultaneous infections, and this will require implementing protocols that yield continuous variables as outputs.

Overall, with viral laboratory testing done from the perspective of the host response, the results of Gencay et al. [1] reported in this edition of the journal provide important new information implicating viral infection as a common cause of acute LRTI. The authors are to be congratulated for completing an elegant study and contributing to the growing body of evidence that viruses deserve their reputation as 'bad news' in the setting of LRTI.

References

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