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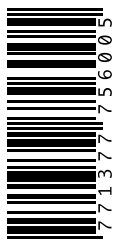
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Molecular diagnostics in respiratory virus infection

Recent trends in virus detection assays and host response biomarkers

This article provides an overview of the recent advances in molecular testing for patients with suspected respiratory tract infection.

New evidence from epidemiological studies

Recent epidemiological studies show that respiratory viruses are the most commonly identified cause of community-acquired pneumonia. In the EPIC study, a large-scale prospective study of an adult U.S. population, researchers found that the incidence of virus-related community-acquired pneumonia (23%) was significantly higher than bacteria-related community-acquired pneumonia (11%) (Jain et al. 2015). The most common pathogens are rhinovirus (9%) and influenza virus (6%), with *Streptococcus pneumoniae* (5%) being the third most common pathogen. Other respiratory viruses are also common among patients with pneumonia, including metapneumovirus, parainfluenza virus, respiratory syncytial virus, coronavirus and adenovirus. Similarly, in a recent meta-analysis respiratory viruses were found to account for 29% of pneumonia cases (Burk et al. 2016). Furthermore, the incidence of viral infection was even higher (44.2%) when the sampling methods included both upper and lower respiratory tract samples, suggesting that the true incidences of respiratory virus infection were most likely underestimated in a majority of studies (Burk et al. 2016). Altogether this evidence challenges the traditional paradigm that bacteria are the most common cause of community-acquired pneumonia.

Technological advance in virus testing

Previously, conventional culture techniques were used to detect common respiratory pathogens. These techniques, insensitive for the detection of viral pathogens, have generated the bacteria-centric view of respiratory tract infection. However, the emergence of novel technology in nucleic acid amplification and multiplex technology has radically changed the diagnostics landscape. New applications of these technologies, such as point-of-care multiplex polymerase chain reaction (PCR) assays, have made it relatively easy and economically viable to test for respiratory viruses in any patients with respiratory symptoms (Chen et al. 2017). It is now possible to detect a wide range of bacterial and viral pathogens in a single sample and the results can be available in just over one hour (Esposito and Principi 2017). Increasing adoption of this point-of-care technology has resulted in an increase in the reported incidences of virus-related respiratory tract infections. This in turn has expanded our understanding of the aetiology of respiratory tract infections.

> ❝ host response biomarkers may serve as a canary in the coalmine even in the absence of virus detection ❞

Evidence supporting point-of-care virus testing

The increasing awareness of respiratory viruses in the aetiology of community-acquired pneumonia, combined with rapid advances in diagnostic technology and molecular testing, have reshaped our thinking and approach to the management of severe respiratory tract infections. The new molecular tools also facilitate the better management of patients with suspected infection. As shown in a recent randomised

Respiratory tract infections are common reasons for admission to intensive care units. For decades conventional culture techniques were the gold standard for establishing the aetiology of the respiratory tract infection. Data generated by these techniques had led to the general belief that bacteria are the most common pathogens in respiratory tract infection. However, a large shift in our thinking on the aetiology of respiratory tract infection has occurred in recent years. This shift is facilitated by the emergence of new data from epidemiological studies and is further propelled by a rapid technological advance in molecular testing, as explained below.

trial, the early detection of a respiratory virus by point-of-care multiplex PCR assay has led to the more timely implementation of infection control measures (prompted by a faster reporting of virus-positive patients), a shortened course of antibiotics and a decrease in the indiscriminate/non-selective use of antiviral therapy (Brendish et al. 2017).

Caveats in virus detection assay

These new diagnostic technologies have a focus on "virus detection", and as such the clinician needs to be aware of the significant drawbacks when applying these assays to patient care. The identification of a virus is an important part of the diagnostic workup. However, without corroborating information on the host response, virus detection by itself has a number of limitations:

(1) "Detection" does not necessarily mean "infection"

Many respiratory viruses detected in virus detection assays are also found in the respiratory tract of healthy humans who do not have symptoms (Hayward et al. 2014; Heinonen et al. 2016). Therefore, the mere presence of a virus in a symptomatic patient does not necessarily mean that the virus is causally related to the presenting illness. For example, both rhinovirus and influenza virus are found in individuals who have no symptoms, as well as those with severe symptoms (Hayward et al. 2014; Heinonen et al. 2016).

(2) Viral load correlates poorly with risk of deterioration

Viral load in the airway does not always correlate with the clinical course of the illness. Patients with a low viral load could have a poor clinical outcome; conversely, patients with a high viral load may not develop a severe illness. It has been postulated that the virus causes the initial local damage in the respiratory tissue, but the subsequent host response triggered by the virus seems to run its own course, independent of the initial virus load (Oshansky et al. 2014).

(3) Transmissibility does not equate to virus replication

The detection of fragments or part of the virus particle usually confirms that the host has been exposed to the virus. However, clinicians should be aware that non-viable virus, dead virus or fragments left behind by a previously active virus can also lead to a "positive" detection test. Detecting fragments of the virus particle (e.g. RNA or antigen) merely indicates the presence of the "footprint" of the virus. Although this confirms that the virus has been transmitted to the host, it does not necessarily mean that the virus is actively replicating, which is an essential prerequisite for tissue injury.

Host response biomarkers as novel diagnostics

Host response biomarkers could provide additional diagnostic information and help
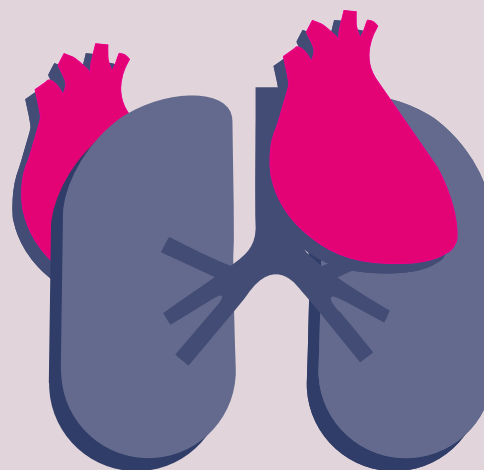
address the limitations of the virus detection assays described above. These biomarkers provide diagnostic information on the state of the activated immune cells and therefore could provide an important link between virus detection and the biology of the host response. The host response of respiratory virus infection typically begins with local tissue injury caused by the invading virus. Soon after this initial event, the viruses set off a chain of downstream immunological events, which, in some individuals, results in disease progression and severe lung injury. This systemic immune response is detectable in the peripheral blood, as measured by the transcriptomic profiling of the peripheral blood ("blood transcriptome"). Recent meta-analysis has found that this transcriptome signature is present in the peripheral blood in most cases of severe respiratory virus infection (Andres-Terre et al. 2015). The clinical utility of using blood transcriptome to assist diagnosis has been recently validated in prospective studies (Tsalik et al. 2016; Zhai et al. 2015; Herberg et al. 2016). Furthermore, a study by Suarez et al. has shown that these transcriptomic biomarkers performed better than conventional biomarkers, such as procalcitonin, in identifying patients with a respiratory virus infection (Suarez et al. 2015).

Combined use of virus detection assay and host response biomarkers

In the future it is envisaged that transcriptomic biomarkers will be used, together with virus detection assay, in the routine diagnostic workup of patients with a suspected respiratory virus infection (Tang et al. 2017). This combined approach has advantages over using virus detection assay alone, as outlined below:

(1) Increased diagnostic yield

The new multiplex viral PCR assays are highly accurate in detecting common virus strains. However, this relies upon (1) an adequate sample of respiratory secretion obtained and (2) the sample is collected during the virus-shedding window. A number of factors could adversely affect this process. For example, viral shedding could be reduced by prior antiviral therapy or sampling could be incorrectly performed, both of which could reduce the sensitivity of the virus detection assay. The host response biomarkers may serve as a canary in the coalmine even in the absence of virus detection and prompt appropriate sampling/further investigations. Thus, the combined use of host response biomarkers and virus detection assay will identify additional cases that would have otherwise been missed by using virus detection assay alone.

(2) Risk stratification

Virus detection assay provides minimal information regarding the risk profile of the infected patient. Risk stratification is clinically important since it allows clinicians to determine which patients should be admitted to hospital or referred to an intensive care unit. Recent studies have shown that host response biomarkers detected in blood transcriptomes correlate well with infection severity in critically ill patients (Scicluna et al. 2017). In the event of a future influenza pandemic, the use of blood transcriptomic biomarkers may assist the triage of high-risk patients and the allocation of limited intensive care resources.

(3) Biomarker-guided immune therapy

Dysregulated host response is a key determinant of outcome in severe respiratory viral infection (Herold et al. 2015; Dash and Thomas 2015). Modulating the host response is currently an area of active research. Novel immune therapy could restore immune homeostasis and therefore halt the progression of severe disease in infected patients (Imai et al. 2016). Given the complexity of the immune response in viral infection, biomarkers are needed to guide the use of such therapy. With an increasing recognition that host response mediates immunopathology in severe respiratory tract infections (Dunning et al. 2014), we anticipate an acceleration of research in this field in the near future.

Conclusion

Future development in this field will most likely consist of the combined use of multiplex virus detection assay and host response biomarkers. With the widespread use of molecular testing in modern laboratories and an increasing recognition of the role of respiratory viruses, intensivists should be aware of the strengths as well as the limitations of these exciting new diagnostic technologies.

Conflict of interest

Benjamin Tang declares that he has no conflict of interest. Maryam Shojaei declares that she has no conflict of interest. Marek Nalos declares that he has no conflict of interest. Anthony McLean declares that he has no conflict of interest. ■

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