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Why diagnose respiratory viral infection?

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1. Introduction

Respiratory tract infections (RTI) are among the most common infectious diseases of humans worldwide, causing significant morbidity and mortality. They are consequently responsible for an enormous economic burden on society in terms of visits to doctors, treatments, hospitalisations and absences from work and school. Upper respiratory viral infections are frequent, with approximately 6–9 infections per year in children and 2–4 infections per year in adults. The actual cost of upper RTI (URTI) is difficult to determine, but included are factors such as over-prescription of antibiotics or absence from work. Lower RTIs (LRTI) are less frequent than upper RTIs (URTI), but between 1 and 13% of patients with LRTI are hospitalised. The cost of these infections is higher. For example, the economic cost of viral LRTI in children was estimated to be over 2.4 billion US dollars annually (Henrickson, 2005).

Clinical diagnosis usually cannot discriminate between causative agents and therefore initial treatment is empirical. It is known that URTI is most likely viral but in the lower respiratory tract there are more than 20 commonly detected bacterial and viral causes of infection. These cannot be distinguished by clinical examination, so require diagnostic tests.. Early diagnosis of the aetiological agent enables effective anti-microbial therapy and other appropriate management of the infection.

Nucleic acid amplification methodologies have revolutionised the diagnosis of infectious diseases. They provide timely, accurate and dependable diagnosis, enabling the initiation of appropriate interventions without delay, improving patient care and ultimately reducing costs. The great strength of molecular techniques, especially multiplexed tests, is that they increase sensitivity and create a means to test for numerous pathogens using a common system. Many of these pathogens were previously unable to be detected by techniques such as DFA and culture.

The clinical impact of rapid diagnosis has mainly been assessed using non-molecular rapid tests. In one prospective study, the impact of timely diagnosis of influenza was examined in patients aged 2 months to 21 years. One group knew the diagnosis for each patient and the other did not. For the unblinded group, there were significant decreases in antibiotic use, number of tests performed, lower associated charges, and a reduced length of stay in the emergency department (Bonner et al., 2003). So far, cost benefit analyses for PCR are limited but we can expect these to appear as molecular assays are implemented.

2. Specific reasons to diagnose infections

2.1. Prognosis

An understanding of the clinical course and the consequences of an infection is extremely valuable. For example, consider a child attending accident and emergency (A&E) with bronchiolitis and there are two pathogens identified: respiratory syncytial virus (RSV) and rhinovirus (RV). Rapid detection of multiple respiratory viruses is only possible by molecular methods. About 70% of infants are infected with RSV during the first year of life, and most children have been infected at least once by the age of two. The initial RSV infection is typically the most severe, causing LRT disease, such as bronchiolotis, in 20–30% of infants. Until recently the prevalence of RV infections in bronchiolitis was underestimated but it is now clear that RV infects the LRT. Molecular techniques for viral diagnosis have increased the evidence that RV is a contributor to bronchiolitis and is probably fairly common. (Jacques et al., 2006). Co-infection with RSV can also lead to more severe illness. In this manner the management of the child would be guided by the diagnosis beyond just supportive care. It has also been suggested that RV as compared to RSV may have a response to anti-inflammatory therapy and that those infected

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with RV, as against those with RSV, should be treated with systemic corticosteroids to reduce recurrent wheezing.

Other situations where the viral diagnosis helps in understanding the prognosis are where an infection leads to hospitalisation or prolongs hospital stay (e.g. pneumonia or severe LRTI). Increasingly it is being recognised that viruses are a significant part of the mixture of pathogens found in pneumonia. For example, a patient in ITU with community acquired pneumonia (CAP) may have *Haemophilus influenzae* isolated but also parainfluenza virus type 2 detected (Templeton et al., 2005). The detection of multiple pathogens may suggest that the pneumonia is more severe and the patient may require a longer stay in ITU.

2.2. Complications of the clinical course

Influenza in a patient with CAP can be complicated with secondary bacterial pneumonia. Although antibiotic treatment is not part of treatment for viral infection it may be started owing to the likelihood of a secondary bacterial pneumonia. Secondary bacterial pneumonia is an important cause of influenza-associated death. Although bacterial therapy is standard, antiviral therapy has been ignored because viral infections usually resolve by the time bacterial pneumonia presents. Scadding reported 7 deaths in series of 19 patients with secondary bacterial pneumonia (a case fatality rate of 37%) (Scadding, 1937) and a paper in the modern era reported 50% mortality (Nicholson, 1998). Thus, the overall likelihood of death from pneumonia in those patients with influenza and a secondary bacterial pneumonia is high and is not affected by antimicrobial efficacy. In a study on mice it was shown by McCullers that treatment of the predisposing influenza virus infection with inhibitors specific for the viral neuraminidase might improve the efficacy of antibiotics and increase survival in persons who are at high risk for complications and mortality during influenza (McCullers, 2004). It is clear that rapid and accurate diagnosis is central to such therapy decisions. Molecular methods are comparable to DFA when a sensitive screen is required within hours of admission into hospital and has the advantage of heightened sensitivity in difficult specimens such as sputum.

Another area where diagnosis has a role to play is with immunocompromised patients where screening of patients prior to stem cell transplants is now performed as part of patient management. If a respiratory virus is detected prior to conditioning then a decision about whether the transplant should be delayed until after the virus has been cleared must be considered (Bredius et al., 2004). In this study, all paediatric haematopoietic stem cell transplant patients were screened using PCR testing for respiratory viruses whether the patients were symptomatic or not. Both symptomatic and asymptomatic patients with viral infections were detected. Using molecular assays as a screening tool to exclude respiratory viruses is also an important part of the diagnosis and management in these patients. There are many respiratory viruses that are best detected by molecular techniques as neither culture nor DFA is efficient. Of particular relevance, immunocompromised patients, especially adults, have been shown to have significant rates of infection with human metapneumovirus (hMPV) (Martino et al., 2005) which is best diagnosed using molecular techniques. Equally important is to make the correct diagnosis in immunocompromised patients presenting with respiratory infection or febrile neutropenia.

2.3. Prevent the spread of disease

Respiratory viral infections are easily transmitted in closed environments. Copious amounts of respiratory secretions increase the chance of infection spread, with children often producing the greatest volumes. The knowledge of which virus or viruses is/are present and who has had close contact may guide use of antiviral agents for prophylaxis or vaccination. If a child with chronic cardiac disease has an increased risk of catching RSV, then palivizumab can be administered to prevent more severe complications from RSV infection. Equally, if parainfluenza virus 3 is detected in a patient to be admitted into a haematology ward then this patient should be isolated to prevent further viral infections in that ward. An outbreak of RSV in a neonatal intensive care unit (NICU) in 2005 led to nine infants being infected before the situation was brought under control and spread stopped. The outbreak cost the hospital over $1.15 million (US dollars), a cost the attending physician felt could have been significantly reduced had RSV been diagnosed as soon as symptoms began to develop. This facility now recommends that all infants in NICU who develop cough, congestion or apnoea should be tested for RSV and other common respiratory viruses during the winter season (Halasa et al., 2005). In the Paediatric ITU in Edinburgh patients are screened twice weekly for all respiratory viruses regardless of symptoms as part of our infection control measures. We have demonstrated that the PCR is positive a few days before symptoms present in immunocompomuised patients with obvious management implications. The cost associated with an outbreak in a paediatric ITU with 11 nosocomial cases was estimated at $83,000 (Serwint and Miller, 1993).

The outbreak of SARS and increasing reports of severe avian influenza are other examples that justify respiratory viral testing as a means to prevent transmission. Rapid diagnosis to detect the presence of SARS CoV or avian influenza would enable appropriate measures to be taken since these infections pose extreme challenges to management in hospitals. The detection of routine seasonal viruses allows alternative diagnosis to be made rapidly as clinically cases related to SARS and other viruses are indistinguishable. Louie et al investigated the most common of pneumonia in patients suspected of SARS and diagnosed normal seasonal viruses in 45% of all suspected SARS cases such that SARS

could be excluded in these patients. Molecular methods (PCR) were employed in this study (Louie et al., 2004).

2.4. Treatment

Early diagnosis of influenza improves the efficiency of prophylaxis or treatment by antivirals and has a strong impact on the cost–effectiveness of curative treatment. Treatment for influenza with the neuraminidase inhibitors needs to be administered within 48 hours of contact, so a diagnosis is required rapidly.

Gonzales et al. (2001) examined antibiotic use for respiratory infection in 1989 in the USA. Based on bacterial prevalence rates for otitis media, sinusitis, pharyngitis, bronchitis and upper respiratory infection, the 'ideal' antibiotic prescription rates were estimated. Out of 41 million antibiotic prescriptions, 22.6 million (55%) were estimated to have been prescribed for infections unlikely to have a bacterial aetiology. Thus, the overuse of antibiotics has a high economic cost. A microbiological diagnosis may have had a significant impact on decreasing excessive and inappropriate use of antibiotics (Gonzales et al., 2001).

Excessive antibiotic use is being increasingly recognised as the main selective pressure driving resistance. In a study investigating outpatient antibiotic use in 26 countries in Europe, there was a shift from the old narrow-spectrum antibiotics to the new broad-spectrum antibiotics and there were higher rates of antibiotic resistance in higher consuming countries (Goossens et al., 2005). One of the consequences of over-prescribing antibiotics, especially to individuals with viral infections only, is that no clinical improvement is observed and the potential risk to cause antibiotic resistance increases. As new antiviral options become available, better treatment choices will benefit the patient and community. Molecular techniques provide timely information regarding the identification of pathogens detected and will guide the clinician's choice of therapy.

2.5. Surveillance and vaccination

Molecular diagnostics play a central role in the surveillance and response of epidemic or pandemic influenza and the circulation of highly pathogenic strains. Real-time assays can be used for diagnosis or surveillance purposes in humans and animals, and microarrays can be used to identify and monitor the spread of dangerous variants. Many countries now have centres in the community that submit samples to the laboratory to gain information on which influenza viral subtypes are circulating in patients and this diagnosis information guides future vaccination policy.

In conclusion, molecular diagnosis of respiratory viruses can deliver timely and sensitive results, detect new and existing viral infections, help understand the roles that pathogens play in a particular infection, guide management regarding treatment and nosocomial transmission and enable surveillance and vaccination strategies to be optimized.

3. Conflict of interest statement

None declared.

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