Influenza diagnosis and management

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Influenza is already an important cause of illness and death each year in Australia and the impact of future pandemics will be many times greater.

Compared with other respiratory viral illnesses, influenza is more severe in itself as well as being more likely to result in complications. These range from milder conditions such as otitis media and sinusitis to acute bronchitis, viral pneumonia and bacterial pneumonia. There are also a number of less common non-respiratory complications, including myocarditis, encephalitis, rhabdomyolysis and nephritis. In addition, a substantial component of severe disease and death from influenza is due to exacerbations of pre-existing cardiac conditions, respiratory disease or diabetes [1]. Accurate diagnosis is the basis of the proper management of patients, understanding of the epidemiology of this virus, and detecting the entry and spread of new influenza strains.

Reliable clinical diagnosis of influenza is difficult. Identifying patients with an influenza-like illness (ILI) is important for guiding investigation and for surveillance purposes, but many patients with ILIs do not have influenza, but one of the many other viruses that cause similar illnesses [2, 3]. The likelihood of influenza is increased where there is a high risk of recent exposure, where the illness is more severe and in unvaccinated individuals, but reliable identification of influenza infections requires diagnostic testing. A confident diagnosis is especially pertinent where the person is at risk of developing, or has already developed, more severe illness, where there are cross-infection issues (e.g. in neonatal or infant wards, or outbreaks in residential care facilities), where it assists in treatment decisions, or as part of a surveillance system [2].

Upper respiratory tract samples collected during the first few days of illness are the most likely to yield the virus. Combined nasal and throat swabs are easily collected and well accepted by patients. Nasal washes (NW), nasopharyngeal swabs and nasopharyngeal aspirates (NPA) are very good samples but require a higher level of training to ensure proper and safe collection.

Recent events with avian influenza and possible pandemics have also required careful thought about the cross-infection risks associated with specimen collection. For samples from these patients, potential aerosol-producing procedures such as NW and NPA should only be done by experienced staff with suitable personal protective equipment and in a physically separated environment [4].

Virus isolation in cell culture remains important to provide influenza strains for monitoring of antigenic change, to detect new strains that may be missed by other methods, to assist in vaccine planning and to allow more advanced characterisation of the virus including confirmation of pandemic strains. Traditional cell cultures may take several days, though the centrifuge-enhanced rapid culture methods using methods are quicker (48-72 hours). Both require laboratories capable of carrying out cell culture and require viable virus in the sample, which can be difficult if specimen transport is delayed or samples are incorrectly stored. While it is essential that sufficient influenza cultures are obtained to meet these needs, cell culture has limitations as a routine diagnostic test.

Antigen detection tests using immunofluorescence (IF) are used widely, especially for testing of NPA. The test can be performed within 2-3 hours of receipt, though usually testing is done on a batched basis once or twice daily. Specimens need to be transported and ideally tested within 1-2 hours of collection to avoid deterioration of the cells.

They are well suited to sampling of young children, who will tolerate the procedure and generally have larger amounts of virus, provided there is a properly trained collector and there is easy access to the testing laboratory. Sensitivity will be lower for adults, for upper respiratory swabs and for samples where there has been suboptimal storage and transport. At the moment, they are not suitable for detection of avian or other newly emergent influenza viruses, as they have yet to be shown to be reliable.

Nucleic acid detection tests are gradually becoming more accessible and are performed in a number of laboratories within Australia. They are the most sensitive tests available for influenza detection, and are as specific as cell culture methods. They can be performed on the full range of respiratory samples, are relatively tolerant of poor storage and transport conditions and can be used for type, subtype and strain identification. With real-time techniques, results can be turned around in 2-3 hours, though testing is generally done on a less frequent batched basis.

Detection is usually targeted at either the matrix gene (which is type specific) or the haemagglutinin gene (which is subtype specific). The latter can be used to determine whether it is one of the currently circulating strains (H1 or H3) or whether it may be avian or human pandemic strains. However, availability is still restricted, methods vary and they are usually more expensive than conventional tests.

A variety of rapid point of care (POC) tests that detect either influenza antigens or neuraminidase activity in throat or nose swabs are now available. Generally, the specificities have been good, so that a positive result is reliable provided that the person has a consistent clinical illness and there is current influenza activity. However, sensitivity can be quite low, usually 70-75% [5, 6]. While some distinguish between influenza A and influenza B, none provide any information about

influenza subtypes, and they cannot be relied upon for either the detection or exclusion of avian or pandemic strains. They have been used to triage patients in emergency departments, for outbreak investigation, to provide access to testing in areas lacking conventional tests, and to assist in decisions about antiviral therapy.

Serological tests are not useful for the acute diagnosis of influenza. IgM detection is not reliable and diagnostic IgG titres do not appear for 1-2 weeks after the onset of the illness [7]. However, they are useful for retrospective diagnosis and to identify patients who have recovered from infection. Traditional methods such as haemagglutination inhibition and complement fixation titres are still preferred, as interpretive criteria for newer methods such as enzyme immunoassays are not well established [7]. Unfortunately, there are currently no readily accessible serological tests for H5N1 influenza, as the traditional methods have limitations and neutralisation titres need to be performed in a high containment laboratory [4].

Quality assurance programmes for virus detection and serological diagnosis are still limited, but it is important that laboratories participate in those that are offered by organisations such as the RCPA quality assurance programmes.

Management of clinical influenza

The key to influenza control is to avoid getting it in the first place. Annual vaccination is recommended, especially for those at risk of severe influenza [8]. Personal hygiene, cough and sneeze etiquette and avoidance of exposure help protect against influenza and other respiratory viruses, as was found in Hong Kong during the SARS outbreak [9].

Antibiotics are used to treat the bacterial complications of influenza, including otitis media, sinusitis and pneumonia. Antiviral agents are now available for the treatment and prevention of influenza – the matrix protein (M2) inhibitors, of which only amantadine is available in Australia, and the neuraminidase inhibitors (NIs) oseltamivir and zanamivir. The NIs reduce the duration, severity and complications of influenza [10]. They can also be used to prevent infection and to control institutional outbreaks of influenza. Their role in the treatment of avian or pandemic influenza is yet to be determined, but they do have a clear role in prevention of infection in the event of a pandemic [4].

As the NIs are active only against influenza and due to the difficulty of clinically diagnosing influenza, there is a role for diagnostic testing to guide treatment.

Unfortunately, antivirals must be delivered within 48 hours of onset of illness, preferably earlier, and this is usually too soon for the results of laboratory-based testing. POC tests have been used to assist and a positive result certainly provides confidence about recommending an NI. However, these tests are not available to many doctors at present. Also, due to the lack of sensitivity of these tests, it may be appropriate to treat even if negative. Recently, the Influenza Specialist Group has produced a set of guidelines for antiviral use, taking into account the likelihood of influenza, the availability of POC tests, the vaccine status and the patient risk of severe influenza [11]. Antiviral agents for influenza are discussed in more detail elsewhere in this issue.

Influenza remains a major threat to human health, both due to threat of new pandemic strains and the ongoing burden of inter-pandemic influenza. Continuing progress in both diagnosis and management will help both individual patients and the public health management of this virus.

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