Common viral illnesses in intensive care: presentation, diagnosis, and management

Craig Johnstone MBChB BSc FRCA
Alison Hall BSc MBChB FRCA FFICM MD
Ian J Hart BSc MBChB PhD FRCPath

Key points
Viral illnesses are increasingly recognized as a cause of major morbidity and mortality in intensive care units.
Recent viral disease outbreaks indicate that a working knowledge of common pathogens, their diagnosis and management is necessary when working in intensive care.
Immunocompromised patients are at increased risk of developing overwhelming viral illnesses.
Early recognition, diagnosis, and treatment are key to successful outcomes.
Early involvement of a medical virologist or medical microbiologist is advised in the investigation, diagnosis, and treatment of suspected viral illnesses.

Early references to viral illnesses are found in ancient Egyptian texts with stone tablet depictions of patients suffering from poliomyelitis. Despite this, early experimentation into viral infections, led by Jenner, did not begin until 1798 with later contributions from Pasteur in the early 1880s. Viruses as a distinct biological entity, however, were not discovered until 1892 when Ivanovsky identified non-bacterial pathogens affecting tobacco plants.1 Subsequent work by Beijerink, Loeffler, and Frosch in 1898 distinguished the tobacco mosaic disease and foot-and-mouth disease agents from pathogenic bacteria and recorded their ‘obligate parasite’ nature.2,3 The first recorded human illness to be confirmed of viral origin was yellow fever in 1901, a discovery made by Reed et al.4 Since then, large numbers of viral pathogens have been identified.

This review does not attempt to be exhaustive but deals with some of the more common viral illnesses that can necessitate ICU admission. Despite this, there remain notable exclusions including arboviruses (which cause viral haemorrhagic fever, zoonotic viruses (including rabies), and the hepatitis viruses, which could in themselves constitute a review article. In cases where rare viruses are the cause for ICU admission and where the patient is immunocompromised, early involvement from a medical virologist or medical microbiologist is required.

Virus characteristics
Viruses have important characteristics with regard to their basic structure. They are very small (30–400 nm) and consist of genetic material (DNA or RNA) contained within a capsid, a coat made up of a number of viral protein molecules called capsomers (Fig. 1). The complete unit of genetic material and capsid is called the nucleocapsid and often has a distinctive symmetry depending upon how the individual capsomers are assembled. Symmetry can be either icosahedral, helical, or complex.

Some viruses consist of a nucleocapsid only, whereas others have an outer envelope that consists of a lipid bilayer of host cell origin into which viral proteins and glycoproteins are anchored. Those viruses without membranes are termed non-enveloped or naked.

The viral protein molecules in the capsid and envelope serve three main functions:
(i) protection of the viral RNA or DNA genome;
(ii) possession of specific sites allowing attachment to the host cell;
(iii) delivery of the viral genome to the interior of the infected cell.

In icosahedral capsids, capsomers are arranged into tight triangular shapes which fit together to form icosahedrons. These package the viral RNA or DNA genomes. In helical capsids, the capsomers are bound to RNA and coiled into a helical nucleocapsid. Only RNA viruses are capable of forming helical capsids. The genetic material inside the capsid can either be DNA or RNA but never both. The viral genome may be linear or circular and either single-stranded (ss) or double-stranded. As viruses lack organelles and ribosomes, they require the apparatus provided by the host cell in order to replicate. The method of replication depends on whether the viral genome is DNA or RNA. The steps involved include adsorption, uncoating of the virus, synthesis of viral structures, and release of virus particles by budding or cell lysis. In doing so, host cells can be subjected to transformation with the induction of oncogenes, latent infection, chronic infection, or cell death.

RNA viruses
Most RNA viruses have ssRNA genomes (though major exceptions include reovirus and birnavirus genomes which are double stranded).
The ssRNA viral genomes are positive (+) stranded or negative (−) stranded. The (+) strand RNA genomes can be translated into protein by the host cell in a similar fashion to messenger RNA (mRNA), whereas (−) strand RNA genomes must first be copied into a positive RNA strand by an RNA-dependent RNA polymerase.

The ss (+) RNA genome of retroviruses is first converted to a double-stranded DNA copy by a unique (viral) enzyme called reverse transcriptase before being transcribed into mRNA and then translated into proteins used for viral replication.

**DNA viruses**

DNA cannot be directly translated into protein and must first undergo transcription into mRNA. Viral DNA genomes are usually double-stranded with the exception of paroviruses (Table 1).

**The RNA viruses**

**Orthomyxoviridae and paramyxoviridae**

These families share the ability to bind to glycoprotein receptors in the upper respiratory tract (URT).

**Orthomyxoviridae**

This family includes the influenza viruses A, B, and C. They are pleomorphic viruses (with spherical and filamentous morphology) with 7–8 (−) ssRNA segments assembled with proteins to form a helical nucleocapsid. It has an envelope with two types of long glycoprotein spikes: one type with haemagglutinin activity (HA) and one type with neuraminidase activity (NA).

The HA spike attaches to sialic acid receptors on epithelial cells of the URT providing a cellular entry route for the pathogen. Sialic receptors also exist on erythrocytes and these viruses can cause agglutination of red cells when isolated and grown in cell culture. Neuraminic acid forms part of the host’s mucinous defence barrier. Neuraminidase on the viral envelope cleaves the terminal sialic acid group from it and other glycoconjugates. This enzymatic activity promotes both entry and release of virus from infected cells.

The three types of influenza (A, B and C) have many strains characterized by antigenic differences in HA and NA. Type A viruses can infect and transmit across a broad host range (humans, mammals and birds), whereas types B and C do not appear to be capable of animal-to-animal or animal-to-human transmission. Type A is the cause of worldwide pandemics, whereas types B and C tend to produce more localized outbreaks and milder forms. Antigenic drift because of minor changes in the NA or HA glycoproteins accounts for epidemics. Antigenic drift tends to lead to less severe disease in individuals pre-exposed to the antecedent virus. Major changes in the HA, called antigenic shift, because of the acquisition of new gene segments can result in pandemics of very severe influenza. This can occur during genetic re-assortment in cells dually infected with a human and an animal virus and hence only occurs with influenza type A.

Influenza virus infection presents non-specifically with fever, myalgia, arthralgia, headache, and cough. The elderly, individuals with chronic disease (e.g. respiratory, renal, liver, cardiovascular disease, or diabetes mellitus), pregnant women, the morbidly obese, and the immunocompromised are at a higher risk of developing complications. Once infected, there is an increased likelihood of developing a secondary bacterial pneumonia, particularly *Staphylococcus aureus* pneumonia. The most recent pandemic in 2009 was due to an H1N1 strain of influenza A. Other pandemics occurred in 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2). The most recent H1N1 outbreak mainly affected 5–24 yr olds, with the obese and pregnant women also at particular risk. Many older patients alive during previous pandemics appeared to benefit from the presence of cross-reactive antibodies against 2009 H1N1. Currently, monitoring of newer H7N9 (Avian flu) strains is ongoing, though sustained human-to-human transmission has not been detected. The source of human infection is unknown but is presumed to be from exposure to infected birds.

The detection of viral RNA by reverse transcription followed by PCR (RT–PCR) is the gold standard diagnostic method for detecting influenza viruses and can be carried out on the nose and throat swabs, nasopharyngeal, tracheal aspirates or bronchial washings.
Highest sensitivity (>90%) of RT–PCR of URT specimens is within 3 days from the onset of symptoms. It usually remains positive after this in patients with ongoing URT symptoms. However, testing URT specimens can give falsely negative results in patients with established viral pneumonia. These patients will usually have lower respiratory tract (LRT) samples positive for the virus so BAL is recommended if clinical suspicion remains high.

Treatment on intensive care is largely focused around organ support. Specific therapies include the neuraminidase inhibitors, oseltamivir, and zanamivir. Most influenza strains are sensitive to these therapies, but resistant strains are beginning to emerge. Current UK guidance states that all patients with complicated influenza infection should receive antiviral treatment. Antiviral treatment should be commenced as early as possible and should be given on clinical suspicion irrespective of the onset of illness and before laboratory confirmation of influenza virus infection. Oseltamivir is to be used for immunocompetent patients. The evidence for use is a reduction in symptoms or disease severity (strongest evidence if started within 48 h of illness onset). Further studies are needed to clarify if there is survival benefit in patients at risk of developing complicated influenza or in patients whom complications have developed. Zanamivir is reserved for patients who are immunocompromised. There is widespread resistance among influenza A viruses to the amantadine class of drugs (amantadine and rimantadine) so they are not recommended for the current circulating strains.

**Paramyxoviridae**

These viruses are structurally similar to the orthomyxoviridae but have ssRNA genomes (not segmented) and the HA/NA are part of the same glycopeptide spike (not two separate spikes). The envelope also contains a fusion protein that causes host cells to form multinucleated giant cells (syncytia).

<table>
<thead>
<tr>
<th>Nucleic acid</th>
<th>Capsid</th>
<th>Envelope</th>
<th>(+) or (−)</th>
<th>Approx. size (nm)</th>
<th>Family</th>
<th>Pathogenic virus/disease example</th>
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<tr>
<td>RNA</td>
<td>Icosahedral</td>
<td>Naked</td>
<td>(+) ss</td>
<td>28–30</td>
<td>Picornaviridae</td>
<td>Poliovirus and other enteroviruses</td>
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<td></td>
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<td>60–80</td>
<td>Reoviridae</td>
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<tr>
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<td>(+) ss</td>
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<td>Rubella</td>
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<tr>
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<td>(+) ss</td>
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<td>Hepadnaviridae</td>
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Common viral illnesses in intensive care
Respiratory syncytial virus
RSV predominantly causes severe disease in children in the first year of life leading to bronchiolitis and pneumonia. It can be particularly severe in premature children, those with chronic lung disease, congenital heart disease, neumomuscular disorders, or immunodeficiency. Prophylaxis with i.m. palivizumab has been considered for high-risk individuals. In the adult population (re-infections), RSV usually causes mild, self-limiting URT symptoms, or flu-like illness. However, it becomes an increasingly recognized cause of pneumonia in the immunocompromised, the elderly (particularly those with chronic lung or heart disease) and residents of long-term care facilities. RSV outbreaks commonly coincide with influenza pandemics. These can go undetected, and the deaths attributed to influenza unless the appropriate laboratory diagnostic tests are used. Infection is confirmed by detecting the viral genome by RT–PCR in URT or LRT specimens (see influenza diagnosis). Aerosolized ribavirin is of benefit in treating RSV infections of the immunocompromised patient but is not used for the immunocompetent. This approach is supported by experience in stem cell transplant populations in whom treatment confers mortality benefit. This may also be the case in other T cell immunosuppressed patients and the use of ribavirin is usually recommended in transplant guidelines (both stem cell and solid organ).

Parainfluenza virus
There are four types of human parainfluenza virus (hPIV 1–4). They usually cause a relatively mild URTI or flu-like illness, though can cause LRTI in the elderly, children, and immunocompromised. It is the commonest pathogen causing croup in the paediatric population. Infection is best confirmed by detecting the viral genome by RT–PCR in URT or LRT specimens. Aerosolized ribavirin may be of benefit in treating hPIV infections of the immunocompromised patient but is not used for the immunocompetent, as is the case in RSV infection.

Human metapneumovirus
Like hPIV, human metapneumovirus (hMPV) usually cause a relatively mild URTI or flu-like illness, though can cause LRTI in the elderly, children, and immunocompromised. Infection is best confirmed by detecting the viral genome by RT–PCR in URT or LRT specimens (see influenza diagnosis). Aerosolized ribavirin may be of benefit in treating hMPV infections of the immunocompromised patient but is not used for the immunocompetent.

Mumps virus
This virus replicates in the URT and local lymph nodes before undergoing haematogenous dissemination to more distant organs. Parotid and testicular swelling are commonly seen with infertility being a rare complication. Both meningoitis and encephalitis can occur, necessitating transfer to an intensive care environment. Rare complications also include sensorineural hearing loss, pancreatitis, myocarditis, thyroiditis, hepatitis, and nephritis.

Diagnosis is on clinical grounds but may be supported by serological tests including the detection of IgM and IgG antibodies, though these are notoriously insensitive. Confirmation is best achieved by RT–PCR of throat, saliva, CSF, or urine samples. Treatment is largely supportive.

Measles virus
Outbreaks of measles, a notifiable disease under the Health Protection Regulations 2010, are commoner in areas where vaccination rates are low. It is highly transmissible, with lots of cases occurring after contact with an index case. During an incubation period of up to 3 weeks where viral replication occurs in the upper respiratory mucus membranes and conjunctiva, there is commonly a prodromal illness of fever, malaise, anorexia followed by coryza, cough and conjunctivitis. This is followed by the emergence of Koplik’s spots (crops of grey/white lesions on the buccal mucosa) and then 2–3 days later the characteristic maculopapular rash. Like mumps, it can then spread to distant organs causing complications including pneumonia, myocarditis, and encephalitis. Subacute sclerosing panencephalitis is a rare and delayed form of measles encephalitis which may present several years after the initial infection with incoordination and mental deterioration.

Diagnosis is on clinical grounds alongside viral RT–PCR from throat, urine or URT/throat and CSF specimens with serological studies (IgM and IgG antibody) if necessary.

Public Health England has published guidance for the use of human normal immunoglobulin to be used within 3 days of exposure for the immunosuppressed and 6 days of exposure for pregnant women and infants under 1 year of age to ameliorate measles disease. Supportive treatment with antibiotics may be required for secondary bacterial infections and isolation precautions are recommended (Table 2).

Retroviridae
HIV infects CD4 T-lymphocytes which can predispose to opportunistic infections often leading to ICU admission. This topic has been reviewed previously and will not be dealt with further here.

Coronaviridae
Most coronaviruses cause mild URTI. However, coronaviruses include the severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) which have received recent publicity. These viruses cause lower respiratory tract disease with high mortality but do not transmit easily from human-to-human. Infection is best confirmed by detecting the viral genome by RT–PCR in URT or LRT specimens. Treatment is largely supportive with no specific antiviral therapy.

DNA viruses
Adenoviridae
These are double-stranded, non-enveloped DNA viruses which can cause respiratory (particularly types 1–7 and 21), gastrointestinal, neurological, and eye infections. There are more than 50
immunologically distinct types. They are remarkably stable in hostile environments allowing them to survive for long periods outside of a host. They spread primarily via the droplet and faeco-oral routes, with infected individuals shedding the disease potentially for months or years after symptoms are clinically resolved. Respiratory infection can lead to croup, tonsillitis, otitis and pneumonia which can be particularly severe in children and the immunocompromised. Nearly 100% of adults have serological evidence of previous exposure. Adenoviruses can cause hepatitis, encephalitis, pneumonia, chronic life-threatening diarrhoea and haemorrhagic cystitis in the immunocompromised. Diagnosis is achieved by PCR of BAL, liver, CSF, or faecal samples. Adenoviral load in blood is useful for initiating pre-emptive treatment with cidofovir to prevent adenoviral disease in heavily T cell immunosuppressed patients (particularly children), but needs to be done weekly over the period when the patient is at risk of developing life-threatening end-organ disease. Treatment of adenoviral diseases is reduction of immunosuppressive therapies where possible and treatment with cidofovir (with pre-hydration and co-administration of probenecid to minimize renal injury). The use of ribavirin is contentious with no consistent evidence of virological response in vivo.

**Herpesviridae**

This family of viruses includes herpes simplex virus (HSV) 1 and 2, varicella–zoster virus (VZV), cytomegalovirus (CMV), human herpes virus (HHV)-6, HHV-7, HHV-8 and Epstein–Barr virus (EBV). Importantly, this group of viruses can establish a latent stage of infection (without any virus replication) but can reactivate from latency to produce an infectious virus again periodically. They express a large numbers of enzymes and other proteins involved in DNA synthesis, virus replication, latency, and immune evasion. The level of virus replication during reactivations is controlled in immunocompetent individuals by the cell-mediated (T cell) immune response. The herpesviridae are subdivided into alpha, beta, and gamma subfamilies. Viral infection by alpha-herpes viruses (HSV 1 and 2 and VZV) causes ballooning of the cells and the formation of multinucleated giant cells leading to cell death in the parabasal and intermediate cells of the epithelium. With cell lysis, clear fluid containing large amounts of infectious virus particles accumulates to form vesicles between the epidermal and dermal layers of skin and mucosal surfaces. Alpha-HSVs can invade and replicate in the CNS and establish latency in dorsal root ganglia. The beta-HSVs group (CMV, HHV-6, and HHV-7) have an affinity for lymphocytes and monocytes and cause infected cells to become enlarged (cytomegaly). The gamma-HSVs (EBV and HHV-8) are also lymphotropic and cause infected cells to become enlarged (cytomegaly). They express a large numbers of enzymes and other proteins involved in DNA synthesis, virus replication, latency, and immune evasion. The level of virus replication during reactivations is controlled in immunocompetent individuals by the cell-mediated (T cell) immune response. The herpesviridae are subdivided into alpha, beta, and gamma subfamilies. Viral infection by alpha-herpes viruses (HSV 1 and 2 and VZV) causes ballooning of the cells and the formation of multinucleated giant cells leading to cell death in the parabasal and intermediate cells of the epithelium. With cell lysis, clear fluid containing large amounts of infectious virus particles accumulates to form vesicles between the epidermal and dermal layers of skin and mucosal surfaces. Alpha-HSVs can invade and replicate in the CNS and establish latency in dorsal root ganglia. The beta-HSVs group (CMV, HHV-6, and HHV-7) have an affinity for lymphocytes and monocytes and cause infected cells to become enlarged (cytomegaly). The gamma-HSVs (EBV and HHV-8) are also lymphotropic and have oncogenic potential. Patients with compromised cell-mediated immune systems can present with severe herpes virus infections.

**HSV 1**

The vast majority of primary infections with HSV 1 are subclinical and antibodies confirm previous exposure in 70–80% of adults. Clinical symptoms in the immunocompetent, when present, include gingivostomatitis, genital herpes, conjunctivitis, keratitis, encephalitis and severe disseminated neonatal HSV infection. In the immunocompromised...
these include pneumonia, hepatitis, colitis and encephalitis which may require organ support. HSV encephalitis presents with pyrexia, altered consciousness, bizarre behaviour, disordered mentation, psychiatric symptoms, seizures and localized neurological signs and must be considered as a potential cause in such patients as it is treatable with aciclovir. Typically CSF analysis will show a clear appearance with a high white cell count (lymphocytes), a normal or slightly raised protein and a normal CSF glucose: plasma ratio. PCR for HSV in CSF will confirm the diagnosis in most patients although it may be negative in the first few days of disease. The mortality is around six times higher in immunocompromised patients. HSV pneumonia can be seen in immunocompromised patients and is best diagnosed by performing HSV PCR of LRT specimens.

HSV is particularly responsive to treatment with aciclovir, a guanine analogue with specific cytotoxicity for HSV-infected cells. This selectivity is, in part, due to the presence of HSV thymidine kinase in infected cells. This activates aciclovir by monophosphorylation, a process that host cell thymidine kinase cannot perform.

**Varicella–zoster virus (VZV)**

This virus causes chickenpox in children and is highly contagious and approximately 90% of adults have been infected. After exposure, the virus infects the respiratory tract and a viraemia then follows with headache, malaise and a characteristic rash starting on the face and trunk before spreading centrifugally, usually developing in crops. Once the vesicles have crusted over and dried up, the patient is no longer considered infectious. It can reactivate from latency in sensory ganglia after periods of stress or reduced cell-mediated immunity. Viral replication and migration along peripheral nerves to the skin then occurs to cause shingles. Diagnosis is usually clinical but can be confirmed by VZV PCR of vesicular fluid.

VZV infection is particularly severe in the fetus, neonates, adults and in immunocompromised patients. It can lead to congenital varicella syndrome, neonatal chickenpox, pneumonia, or encephalitis which may require ICU support. In the UK, guidance recommends that both pregnant women and immunocompromised patients should be offered varicella–zoster-immunoglobulin (VZIG) within 10 days of exposure. This is a pooled plasma product with a good safety profile. Prophylaxis with oral valaciclovir is an option if VZIG cannot be given (1 g tds 7 days after the first day of contact for 7 days). Treatment of life-threatening VZV infection and disseminated shingles is with i.v. aciclovir. Oral valaciclovir (1 g tds) may be used for uncomplicated shingles or chickenpox for 7 days or for the immunocompromised continue until 48 h has passed without new vesicle formation.

**Cytomegalovirus (CMV)**

This can cause four main infectious states.

(i) Asymptomatic infection: this is common with approximately 80% of all adults having antibodies against CMV.

(ii) Placental transfer of CMV: this occurs in 40% patients after primary CMV infection in pregnancy and congenital CMV infection can lead to severe fetal brain damage, or less severe damage, such as sensorineural hearing loss and intellectual impairment, only identified months or years after birth or completely asymptomatic.

(iii) Infectious mononucleosis can occur with a similar presentation to that caused by EBV.

(iv) Reactivation in the immunocompromised patient: this is the commonest reason for patients to require ICU admission. This can lead to disseminated infection or localized disease such as retinitis or pneumonia in HIV patients, once the CD4 count decreases <50–200 cdμl⁻¹, patients can develop CMV retinitis, but pneumonia is rare. This is in contrast to bone marrow transplant patients who are at high risk of developing CMV pneumonitis with lower incidence of retinitis.

Serological tests can be used to identify CMV infection. IgM antibodies usually appear within a week of infection followed 1–2 days later by an increase in IgG levels. IgM subsequently decreases to low or undetectable levels over a few months, whereas IgG levels will remain detectable life-long, indicating previous infection. CMV-PCR can also be used to detect CMV infection using blood, saliva, urine, and other bodily fluids. The detection of CMV in damaged tissue is required to confirm CMV end-organ disease. Histology can also confirm active CMV infection by identifying basophilic intranuclear ‘owl’s eye’ inclusions.

Treatment with ganciclovir, a nucleoside analogue (5 mg kg⁻¹ i.v. for 2–4 weeks) is usually used for immunocompromised patients with life-threatening end-organ disease. I.V. foscarnet, a phosphonic acid derivative which inhibits viral DNA polymerases, can also be used for ganciclovir-resistant CMV.

Universal infection control precautions should be followed (Table 2) for all healthcare workers having contact with patients shedding CMV in body fluids, including previously unexposed pregnant women as primary CMV infection can sometimes lead to congenital CMV infection in the fetus.

**Epstein–Barr virus (EBV)**

This virus infects human B-cells and commonly causes the primary self-limiting illness infectious mononucleosis. It is characterized by fever, pharyngitis, headache, malaise, and lethargy which can be accompanied by lymphadenopathy and splenomegaly. Rarely, meningitis, encephalitis, haemolyisis, and splenic rupture can occur. It can also predispose to the development of Burkitt’s lymphoma and nasopharyngeal carcinoma in certain circumstances. In the immunocompromised and post-transplant population, an EBV-driven lymphoproliferation also known as post-transplant lymphoproliferative disease (PTLD) can occur.

The diagnosis of infectious mononucleosis is often suspected when atypical mononuclear cells are found in peripheral blood films. The virological diagnosis can be confirmed serologically by detecting heterophile antibodies or EBV IgM antibodies.

Antiviral treatment of infectious mononucleosis is not advocated as the disease is usually self-limiting, though corticosteroids may be used in cases where there is significant neurological involvement, haemolysis or thrombocytopenia.
Summary

Viral illnesses frequently present with non-specific symptoms which can lead to delays in diagnosis and treatment. Primary presentation with viral-like symptoms may also reflect opportunistic disease in the immunocompromised patient. Close liaison with a medical virologist or medical microbiologist is advised for specimen collection, investigation, interpretation of results and antiviral treatment of patients with suspected viral illnesses as virus detection in the immunocompromised is not always indicative of disease. The prompt investigation, diagnosis and antiviral treatment of such illnesses are key to good outcomes in terms of both morbidity and mortality. Finally, the prevention of infection by immunization, antiviral prophylaxis, and infection control are equally important in the general management of viral infections both in the community and in healthcare facilities. The diagnosis, management and infection control precautions are summarized in Table 2.14

Declaration of interest

None declared.

References


Please see multiple choice questions 13–16.