Management of Viral Infections in ICU

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Key Points
Viral infections, ICU.

15.1 Introduction

The modern day diagnostics have enabled the physicians to recognize viral infections in intensive care units more often. Many critical illnesses are being increasingly attributed to viral etiologies, in both community and hospital settings. Hitherto, it was believed that only immunosuppressed patients are afflicted with viral infections with severe outcomes. However, it has been progressively recognized that immunocompetent patients, especially with certain risk factors, may also get admitted to intensive care units with critical illnesses attributable to viral infections. Even though respiratory system involvement is most common, a neurological, cardiovascular or a multisystemic presentation may also be seen. An astute intensivist may recognize that a worsening in clinical status of patients admitted in intensive care units may be due to reactivation of certain viruses. It is imperative to think about viral infections, as a possible etiology and a differential diagnosis, in critically ill patients with new onset fever, failure to wean or multiorgan dysfunction. An inadvertent misdiagnosis of the etiological agent will translate into poor
outcomes. Hence, it is indispensable to train the intensivist for early suspicion, diagnosis and management of viral illnesses in intensive care units. The aim of the present chapter is to sensitize the intensivist about viral infections which have the potential to cause life threatening illnesses requiring management in critical care units.

15.2 Epidemiology/Problem Statement

Viral infections are common self-limiting illnesses, which may quite often go unnoticed in a community. On the contrary community acquired viral infections may also lead to life threatening manifestations in patients with certain risk factors, which may require intensive care management.

Respiratory viruses may be held accountable for 5–10% of patients with community acquired pneumonia (CAP) and one third of patients with severe pneumonia. Even though influenza virus (type A and B) and rhinovirus are the most common virus isolated, these are still underdiagnosed in critically ill patients. The other respiratory viruses which may cause CAP are parainfluenza, rhinovirus, adenovirus, respiratory syncytial virus (RSV), coronavirus, and human metapneumovirus. Community acquired pneumonia (CAP) due to these viruses may progress on to develop acute respiratory distress syndrome (ARDS), the exact incidence of which is not yet known. Cytomegalovirus (CMV), influenza (human, avian, swine), and adenovirus are the 3 most common causes of severe viral CAP in immunocompetent adults. A new addition to the list of viruses is the SARS-CoV-2, the etiological agent for COVID-19 described recently. Around 40% of acute exacerbations of chronic obstructive airway disease (COPD) leading to cardiorespiratory failure and ICU admissions have been documented to be caused by respiratory viruses. Significantly, 16–49% of patients with acute respiratory failure or unspecified lower respiratory tract infections needing critical care management have viral etiologies. Respiratory viruses may even be isolated in 39% of critically ill patients with polymicrobial infections.

Similarly nosocomial reactivation of latent viruses, like Herpes virus (HSV) and CMV, may progress on to develop a severe illness in already critically ill patients, ranging from unexplained fever to weaning failure. Other than herpesviridae group of viruses influenza, parainfluenza, rhinovirus, metapneumovirus, RSV, and adenovirus may also be accountable for nosocomial infections in critically ill patients. Acanthamoeba polyphaga mimivirus (mimivirus) has been hypothesized as a possible etiological agent for nosocomial ventilator associated pneumonia (VAP). However, there is not enough evidence so far to support this hypothesis. Fortunately observational studies have shown that the respiratory viruses have a very limited role to play as a causative agent for nosocomial pneumonia. It has been reported that only <5.5% of critically ill patients on mechanical ventilator develop VAP, due to one of the respiratory viruses.
Cytomegalovirus infection is common in community with increasing seroprevalence with age of infected individuals. The seroprevalence of CMV infections increases from 65% in the fourth decade of life to 91% in ages more than 80 years. Among critically ill patients, 0–36% may develop CMV infection, which may be primary or reactivation. Higher incidence of reactivation is seen in septic patients with high disease severity and ICU stay more than 5 days. Similarly, 45–56% of burn patients may demonstrate fourfold rise in serological titers of CMV or CMV viremia suggesting reactivation. Cytomegalovirus infection develops mostly between 4 and 12 days after ICU admission. The highest viremia in patients requiring intensive care is seen after a median stay of 26 days in ICU. Even though CMV infection may be asymptomatic in immunocompetent, it leads to unexplained fever, infectious mononucleosis like presentation, severe CAP, and postperfusion syndrome in critically ill patients.

It has been observed that HSV bronchopneumonitis, just as CMV, involves critically ill patients who are being mechanically ventilated, with ARDS, with burns or after surgery. Herpesvirus may get reactivated in about 54% of patients who are being mechanically ventilated. This reactivation usually takes early during the stay in ICU. Interestingly, 56% of these patients with HSV reactivation are asymptomatic and the remaining may be associated with gingivostomatitis or herpetic ulceration of the lip. Herpesvirus bronchopneumonitis usually occurs in patients on mechanical ventilation after a mean of 14 days. Even 21% of patients with VAP and 30% of patients with ARDS may be attributed to herpesvirus.

Many a time, isolation of viruses does not mean causal association. Isolation of these viruses in critically ill patients is usually associated with higher mortality rate which is similar to that of bacterial infections. It is still not clear whether these outcomes are directly related to viral etiology or they are just a marker of disease severity.

The etiologies of acute encephalitis syndrome include infectious and noninfectious etiologies. The infectious etiologies include viruses, bacteria, fungi, and parasites. The viruses responsible for acute encephalitis syndrome (AES) in India have been tabulated as follows (Table 15.1).

Herpesvirus is one of the most common viruses causing sporadic encephalitis. In India, Japanese encephalitis (JE) virus is the most common virus causing acute encephalitis in northern, northeastern, and southern India. It has been estimated that approximately 7500 annual JE cases may be seen in India in the event of an epidemic, with a morbidity rate of 0.3–1.5 in a population of 1,00,000.

| DNA viruses | HSV, VZV, HHV 6, EBV, adenovirus, parvovirus, CMV |
| RNA viruses | JE, WNV, dengue, CHIKV, enterovirus, MMR, chandipura, Nipah, KFD, rabies, HIV, LCMV |

**Table 15.1** Viruses causing AES

HSV herpesvirus, VZV varicella zoster virus, HHV 6 human herpesvirus 6, EBV Epstein Barr virus, CMV cytomegalovirus, JE Japanese encephalitis, WNV west Nile virus, CHIKV chikungunya virus, MMR measles-mumps-rubella, KFD Kyasanur forest disease, HIV human immunodeficiency virus, LCMV lymphocytic choriomeningitis virus
As far as viral hemorrhagic fevers are concerned, India is endemic to dengue and Kyasanur forest disease. Dengue fever is found to occur throughout the country except some higher mountainous reaches. Kyasanur forest disease (KFD) is found to occur predominantly in the 5 districts of Karnataka state, namely Shimoga, Chikkamagalore, Uttar Kannada, Dakshina Kannada, and Udupi. Seasonal outbreaks of KFD are known to occur from January to June. Epidemiological investigations have found seropositivity for KFD from neighboring states of Tamil Nadu and Kerala as well. Recently, an outbreak of Crimean–Congo hemorrhagic fever (CCHF) was noted to occur in Ahmedabad where four deaths were reported due to this hemorrhagic fever. Hantavirus has also been occasionally reported from few parts of the country. Thottapalayam virus, the first hantavirus, was reported from Vellore in the year 1964. Seroepidemiological studies from Southern India have found out that 14.7% of fever cases may be positive for hantavirus serology. Among the healthy blood donors, 5.7% were positive for hantavirus in the same study.

15.3  Approach to the Patient

The clinical features of viral infections in the ICU are nonspecific and very similar to those of bacterial or fungal infections. Thus, a very high index of suspicion may be required to consider viral infection as a differential diagnosis. It is imperative to make an etiological diagnosis so as to provide targeted therapy to the critically ill. Lately, the targeted microbiological investigations have reduced the uncertainties in making a diagnosis.

Certain clinical variables may predict the possibility of viral etiologies, such as immunosuppressed status, use of corticosteroids >10 mg/day for 3 weeks, use of other immunosuppressives, ground glass attenuations on pulmonary CT scans, increased duration of hospital/ICU stay, mechanical ventilation, and late onset VAP. Out of these, immunosuppression and ground glass attenuation are most prominent on multivariable analysis.

The intensivist should consider screening for CMV in all critically ill patients with fever and involvement of one or more organs, with no other explanation for their clinical status. Patients with unexplained ARDS and pneumonia should be evaluated for HSV and CMV infections. Clinicians should remember the possibility of HSV pneumonia/HSV associated ARDS, in appropriate patients, if they have associated herpes labialis or gingivostomatitis. All acute respiratory infections should be evaluated for influenza virus during influenza season. HSV may get reactivated due to trauma of intubation or mechanical ventilation. This may later lead to late onset VAP, which may present as unexplainable weaning failure. Unlike HSV associated late onset VAP, late onset VAP attributable to CMV occurs very infrequently. Critically ill patients with ground glass opacification on pulmonary CT scans, in appropriate settings, should be assessed for respiratory viruses. Besides, the viral etiologies may be considered in clinical settings other than mentioned here, if deemed fit by the treating clinician. An algorithm regarding approach to viral CAP is suggested in this review (Algorithm 15.1).
The viral infections are usually self-limiting, however, they may have worse outcomes in critically ill patients with risk factors. Outcomes of viral infections in critically ill patients may be similar to those of bacterial infections. These two groups of patients may have similar 28 days mortality rates, severity of illness, duration of mechanical ventilation or duration of ICU stay. However, patients having both bacterial and viral respiratory infections may end up with worse disease severity than patients with only one of them. Hence, even after identification of a virus, concern about a bacterial coinfection still persists. This concern makes it difficult for the clinician to limit use of antimicrobials.

### 15.4 Clinical Features

As already mentioned, viral infections have nonspecific clinical presentations which may be difficult to differentiate from bacterial or fungal infections. Even the severity and clinical course of viral respiratory infections is comparable to that of

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**Algorithm 15.1 Approach to viral community acquired pneumonia**

| Severe community acquired pneumonia |
|------------------------------------|
| Rule out noninfectious causes – pulmonary embolism, CHF, pulmonary drug reactions, pulmonary hemorrhage, collagen vascular diseases (SLE pneumonitis, sarcoidosis), clinical decompensation of pre-existing ILD |
| Note presence and distribution of infiltrates in chest X ray |
| Focal/segmental/lobar pulmonary infiltrates |
| • consider bacterial CAP – 2 most common bacterial pathogens – S Pneumoniae, Legionella |
| • Leukopenia, relative lymphopenia, thrombocytopenia, mildly increased transaminases, conjunctival suffusion, lobar infiltrates – adenoviral CAP |
| No/minimal pulmonary infiltrates or bilateral symmetrical pulmonary infiltrates – HIV infected patients with PCP, immunosuppressed patients, patients with viral pneumonia (influenza, SARS, hantavirus pulmonary syndrome, CMV) |
| Leukopenia, lymphopenia, thrombocytopenia, mildly increased serum transaminases – seasonal influenza, swine influenza. |
| Atypical lymphocytes with leukopenia, lymphopenia, thrombocytopenia, mildly increased serum transaminases – CMV |

Note presence and distribution of infiltrates in chest X ray
bacterial and fungal infections. Immunocompromised patients have a more complicated course of illness as compared to immunocompetent. Whereas, an “atypical” pneumonia presentation may be seen in immunocompetent, severe lobar or bilateral pneumonia may be seen in immunocompromised hosts. These infections may be acquired either in community or nosocomial settings. The respiratory virus profile in these two settings is different as detailed in the following table (Table 15.2).

The respiratory viruses are responsible for many of the community acquired infections. Patients afflicted with respiratory viruses present with nonspecific complaints. The nonspecific symptoms may include fever, chills, arthralgia, myalgia, headache, vomiting, diarrhea, otitis, tonsillitis, keratitis, and conjunctivitis. The respiratory symptoms may comprise of cough, rhinorrhea, and shortness of breath. There may be extra pulmonary involvement as well, such as inappropriate secretion of antidiuretic hormone, neurological abnormalities, hepatitis, encephalitis, meningitis, transverse myelitis, Guillain–Barré syndrome, and myocarditis. In particular, hemorrhagic cystitis may be found with adenoviral affliction mostly in immunosuppressed. Herpes simplex virus may have associated gignonvostomatitis, keratitis, conjunctivitis, herpetic lip ulcerations, and genital herpes. The respiratory viruses usually lead to a self-limited mild illness in immunocompetent patients, which may quite often go undetected. On the contrary, fulminant forms of viral pneumonia may be seen in certain category of immunosuppressed patients with risk factors, such as morbid obesity, diabetes, pregnancy, hemoglobinopathy, atherosclerotic disease, congestive heart failure, asthma, cystic fibrosis, COPD, cirrhosis, and chronic renal failure. Significantly, patients with CMV associated community acquired pneumonia (CMV-CAP) may present with long standing fever without any prominent respiratory symptoms. Thus, a high index of suspicion is required to diagnose CMV-CAP. Associated hypoxemia may be present in severe viral CAP. Many of these presentations will require organ support in ICU settings.

As against the community acquired infections, nosocomial viral infections in the intensive care unit are usually caused by reactivation of viruses like herpes virus (HSV), Epstein Barr virus (EBV), and CMV. These viruses can get reactivated in critically ill patients with one or more of the following risk factors—mechanical ventilation, bacterial pneumonia, corticosteroid use, sepsis, shock, burn, trauma, blood transfusion, postsurgery, chronic renal failure, and extremes of age. Reactivation may be followed by a disseminated or a localized disease. Even though HSV reactivation in throat happens in early ICU admission HSV induced bronchopneumonia happens later, after about a mean of 14 days of mechanical ventilation. These patients will have symptoms such as fever, hypoxemia, and purulent tracheal secretions. Reactivation of CMV in critically ill patients with any one of the
discussed risk factors may lead to severe manifestations or multivisceral involvement. The spectrum of systemic involvement due to CMV infection in critically ill patients includes interstitial pneumonitis, hematological disorders, hepatitis, gastroenteritis, colitis, myocarditis, meningoencephalitis, uveitis, and retinitis. The lung involvement is the most common. Transfusion associated CMV mononucleosis is one of the causes of new fever in critically ill adult patients. The median time to onset of CMV infection varies between 4 and 28 days. Epstein Barr Virus (EBV) may also show reactivation in critically ill patients after ≥5 days. In immunocompetent individuals EBV may present with fever, pharyngitis, headache, malaise, lethargy and may have associated lymphadenopathy and splenomegaly. Meningitis, encephalitis, hemolysis, splenic rupture may occur rarely. There are not many studies looking into the clinical presentation of EBV reactivation in critically ill patients. It has been suggested that EBV and CMV reactivation should be entertained as a cause of fever in critically ill patients without any specific fever related symptoms and with no response to conventional therapy. Similar to community acquired infections, nosocomial infections may also result in grave outcomes in immunosuppressed and critically ill immunocompetent patients. HSV and CMV may be isolated from mechanically ventilated patients and is associated with prolonged mechanical ventilation, ICU stay and increased mortality rate. Reactivation of EBV is associated with increased morbidity and mortality. Higher viral loads have higher incidences of these complications. However, a causal association between infection and poor outcomes has not been convincingly proven so far.

Complications may be seen more frequently in patients with risk factors. Besides, late consultation, lower respiratory tract lesions, and leukopenia are also associated with severity in H5N1 infections. Both community acquired and nosocomial viral infections may lead on to the development of ARDS. The “common” viruses which may cause ARDS include influenza viruses (H1N1, H5N1) and coronaviruses. Uncommonly, viruses causing nosocomial pneumonia such as HSV and CMV may also progress on to ARDS. Diffuse viral pneumonitis with severe hypoxemia/ARDS may be associated with shock, hepatic failure, and renal failure. Rapid worsening may be seen in influenza on day 4 or 5, with intubation often required within 24 h of admission. CMV infections in an immunocompetent patient may have complications such as thrombosis, disseminated intravascular coagulation (DIC) due to hemostatic abnormalities and portal venous thrombosis due to acute hepatitis. Immunomodulatory effects of CMV may lead to increased incidence of fungal and bacterial opportunistic infections (Tables 15.3 and 15.4).

15.4.1 Viral Infections of the Nervous System in the ICU

Viral infections of the central nervous system may cause any one of the following neurological syndromes—encephalitis, meningitis, meningoencephalitis, myelitis, polyradiculoneuropathy, Guillain–Barré syndrome, subacute sclerosing panencephalitis, and postinfectious acute disseminated encephalomyelitis. Patients with clinical features like seizures, altered sensorium, coma, and respiratory failure (due to
aspiration, neuromuscular weakness, and atelectasis) will require ICU support. Other clinical manifestations include fever, bizarre behavior, headache, disordered mentation, psychiatric symptoms, and localized neurological signs.

### 15.4.2 Viral Myocarditis in the ICU

Patients with viral myocarditis present with clinical signs and symptoms suggestive of congestive heart failure. Low perfusion state due to shock may lead to end organ damage, which in turn will need ICU management of patients.

### 15.4.3 Viral Hemorrhagic Fever in ICU

Clinical manifestations of viral hemorrhagic fever ranges from mild to life threatening illness. The symptoms include abrupt onset of fever, diffuse body aches, headache, malaise, nausea, vomiting, diarrhea, conjunctival suffusion, photophobia, and abdominal pain. Hemorrhagic rashes and bleeding manifestations may be seen in severe disease. Shock and resulting hypoperfusion leads to target organ failure, resulting in worse outcomes. Severe disease may see organ involvement like hepatitis, encephalitis, ALI/ARDS, pulmonary edema, diffuse alveolar hemorrhage, and meningitis. Dengue fever is identified with the help of characteristic plasma leakage which may lead to fluid accumulation in pleural and abdominal cavities. The case fatality rate may range from 50% in hantavirus pulmonary syndrome to <1% in dengue hemorrhagic fever.
Since viral infections have a very nonspecific presentation, a very high index of suspicion is required to consider a possible viral etiology among a wide list of differential diagnosis. This suspicion will need confirmation with the help of certain investigative modalities. Even among the available investigations, hematological, biochemical, and radiological modalities may have nonspecific findings. In this scenario, the targeted microbiological investigations (viral isolation, detection of the virus by PCR or antigen assays, viral serology, and/or viral cytopathic effects) hold the key to the final diagnosis of a viral etiology. It may be not enough to hold the virus responsible for the clinicopathological condition by its mere presence in the evaluated samples. The definitive evidence in favor of a causal association between the virus and the clinicopathological entity is the demonstration of “defining” cytopathic effects. However, this may not always be achievable in real life conditions.

Samples for targeted microbiological evaluation will depend upon the primary organ involved as highlighted in the following table (Table 15.5).

It is important to collect the appropriate samples in adequate amounts for processing, in order to achieve the best possible diagnostic returns. For instance, the sensitivity of the nasopharyngeal swabs and bronchoalveolar lavage (BAL) is better than the nasal swabs for detecting respiratory viruses. Hence, these methods may be preferred over the nasal swabs for diagnostic purposes.

We will now discuss each one of the microbiological methods with its advantages and limitations as follows

1. **Viral PCR assays**—This form of investigation is being considered as gold standard because it is rapid and highly sensitive to pick up minute viral nucleic acids in the appropriate clinical samples. This modality may be utilized to diagnose any of the viral infections. The highest sensitivity of PCR assay to diagnose influenza in upper respiratory tract (URT) samples is within 3 days from the beginning of symptoms. However, clinicians should remember that URT samples may be falsely negative in patients with established viral pneumonia, wherein evaluation of BAL may be preferred. RT-PCR detects CMV in blood samples after a median ICU stay of 12 days, with the highest viremia being detected after a median of 26 days in the ICU. The exact schedule of testing to
detect CMV reactivation remains to be ascertained for nonimmunocompromised patients as against a weekly assessment in immunocompromised. Adenovirus infection may be diagnosed by PCR assays of BAL, liver, fecal or CSF samples. However, in the absence of relevant symptoms, positive PCR assays of the respiratory secretions and fecal samples may signify viral shedding and not acute adenoviral infection. This modality remains the preferred diagnostic modality for avian influenza, RSV, parainfluenza virus, herpes simplex virus, human metapneumovirus, herpes zoster, and coronavirus also. Quantitative PCR analysis may also help in predicting prognosis as higher viral loads are related to higher mortality rates and declining viral loads on treatment underscores response to therapy. Higher viral loads will also favor the possibility of active infection rather than latent infection. The limitations of PCR assay include non-standardization and higher cost of commercially available systems. It will also not help to differentiate latent from active infection.

2. **Viral antigen detection**—This method is advantageous over shell vial cultures because of its rapid turnover and higher sensitivity and specificity. Recognition of pp65 antigen from peripheral blood leukocytes utilizing monoclonal antibodies is one of the preferred diagnostic modalities for diagnosis of CMV infections. The consecutive samples may be interpreted for serial rise in CMV antigen titers to identify CMV reactivation as against latent infections. However, the sensitivity of this test requires sufficient leukocytes to be present in peripheral blood film. Detecting viral antigens is laborious and requires instant processing of samples. Apart from these limitations, this is a highly subjective test which requires rendition of an expert microscopist.

3. **Viral serological methods**—This methodology may be utilized to diagnose CMV and EBV infections. CMV infection encountered in ICU patients is mostly reactivation of an old infection rather than being a primary infection. In this scenario, an active CMV infection is confirmed with the demonstration of CMV specific IgM antibodies along with four fold increase of IgG titers in paired sera. Singular elevation of IgM titers may highlight a primary infection or a false positive test in presence of either a HHV6/EBV infection or rheumatoid factor positivity. Similarly, false negative tests may also occur in the presence of rheumatoid factor. Hence if the clinical presentation and serological tests for CMV are discordant, then rheumatoid factor, IgM EBV and IgM HHV 6 should be evaluated in order to rule out false positive and negative tests. EBV infections may be suspected in the presence of heterophile antibodies and/or EBV IgM antibodies.

4. **Viral isolation**—The virus may be isolated utilizing tissue culture or shell vial culture practices. It used to be considered as a gold standard before the advent of PCR assays. However, it has become obsolete now due to its low sensitivity and specificity. Besides, it is laborious and the results may take up to 14 days to become available. In particular, CMV viruria may signify primary infection or long-term asymptomatic virus shedders following a primary infection. Hence interpretation of CMV viruria requires a proper clinical assessment to rule out other differential diagnosis.
5. **Viral cytopathic effects**—The recognition of cytopathic effects in the viral culture supports a diagnosis of acute as against a latent viral infection. The CMV cytopathic effects include cytomegaly, intranuclear basophilic inclusions surrounded by a clear halo (giving them a typical appearance of an owl eye) and clusters of intracytoplasmic eosinophilic inclusions. The CMV cytopathic effects occur very slowly and may resemble HSV in first 1–2 days. The CMV culture needs to be observed twice a week to record typical cytopathic effects for at least 3 weeks before reporting it as negative. The nuclear and cytoplasmic inclusions are specific for HSV and CMV infections, respectively. This technique requires a skilled intensivist and a pathologist. Thus, PCR assays are preferred over this technique at present.

Apart from the targeted microbiological investigations, CSF analysis and chest X ray may also help in diagnosis making as explained below.

**Chest X Ray** The chest X ray may show abnormalities in patients involved with one of the respiratory viruses such as bilateral basilar patchy or interstitial infiltrates. These infiltrates usually subsides slowly over a period of 6 weeks. However, these abnormalities are nonspecific and are not peculiar for any of the viruses. Thus the chest X ray, at best, helps to exclude differential diagnosis such as typical or atypical bacterial pneumonias.

**CSF** The CSF may require evaluation in patients with clinical presentation suggestive of meningoencephalitis. The CSF is usually clear with a high lymphocytic white cell count, normal glucose levels and a normal to raised protein levels. Of note, lymphocytic pleocytosis is also noted in tubercular, fungal or partially treated meningitis. Polymorphonuclear leukocytes in CSF signifies bacterial meningitis, or these may also be found in early entroviral, WNV, arboviral or CMV infections. Decreased CSF glucose levels are found in meningoencephalitis due to entrovirus, mumps, VZV, LCMV, and HSV. PCR assay of the CSF helps to determine the culprit virus after the first few days of illness.

Of note, other hematological and biochemical investigations are usually nonspecific and they do not help to make a diagnosis on their own. These may include relative lymphopenia or atypical lymphocytes, associated with other biochemical abnormalities such as mild elevation of serum transaminases in liver function tests. The atypical lymphocytes on the peripheral smear may help to recognize infectious mononucleosis like syndrome in CMV and EBV infections. Leukopenia, thrombocytopenia, deranged prothrombin time, and raised D-DIMER levels will support a diagnosis of viral hemorrhagic fever. Hemoconcentration and rising hematocrit levels are characteristically seen in dengue hemorrhagic fever. The hemorrhagic fevers can be diagnosed and the culprit virus identified, by subjecting the serum or any infected tissue to antigen detection by antigen capture ELISA, serology, RT-PCR or cell cultures as discussed above.
15.6 Management

Management of viral infections in ICU settings begins with infection control. Apart from universal infection control practices, care should be taken that open suction systems, endotracheal intubation, BiPap, nebulizers, and ventilation systems do not spread infections in the critical care settings. Disinfection should be routinely employed as it is highly active against most of the viruses. Other infection control measures to control transmission by airborne droplets and by contact should be part of every ICUs routine practice. Isolation may be required in viral hemorrhagic fevers and influenza. Of note, isolation is recommended in avian influenza, even though the human to human transmission is not very common. Most of the viral infections require supportive management, however, specific therapies may be available for some of them.

15.6.1 Supportive Management in Viral Infections

15.6.1.1 Viral Infections of the Nervous System

Mostly these infections requires supportive therapy which includes management of cerebral edema, high intracranial pressure, hypoxemia, low cerebral perfusion pressure, fever, and seizures. These associated complications require urgent identification and management as they may worsen underlying neurological damage.

15.6.1.2 Viral Infections of the Respiratory System

The management is largely supportive and includes dealing with the associated complications. Many of the complications such as pneumonia, adult respiratory distress syndrome, asthma/COPD exacerbations, and restrictive lung disease due to Guillain–Barré syndrome may end as hypoxic and/or hypercapnic respiratory failure. This will require appropriate respiratory supportive management and ventilatory (invasive and noninvasive) strategies. In particular, management of ARDS will include protective ventilatory strategies such as prone positioning, low tidal volume, high PEEP, recruitment maneuvers, high frequency oscillation ventilatory strategy, and extracorporeal membrane oxygenation [ECMO]. Utilization of ECMO has improved outcomes and 60–70% of patients may survive to get discharged from hospital.

15.6.1.3 Viral Myocarditis

Severe cases may require mechanical ventricular assist device support, as a bridge therapy until patient improves or until transplantation is possible.

15.6.1.4 Viral Hemorrhagic Fever

Notification of these cases is a must to alert the local and national public health officials. Immediate isolation of the cases, even if suspect, is required for infection control and for preventing transmission. Significantly, no specific treatment modalities are available and so only supportive care is possible. Corticosteroids should not be used.
15.6.2 Specific Management of Viral Infections

The specific antiviral therapies may be needed, as soon after a diagnosis, in only a few handfuls of viral illnesses.

15.6.2.1 Specific Therapy for Respiratory Infections

(a) Influenza (H1N1/H5N1)—Out of neuraminidase inhibitors (NAI) and amantadine groups of antivirals, the latter are no longer preferred on account of high resistance to these drugs. Oseltamivir is indicated in severe infections or in areas endemic with strains having high mortality (e.g., H5N1). In these instances, antiviral therapy may be provided on clinical suspicion alone even without any laboratory confirmation. On the contrary, their use in nonsevere patients should be discouraged because of fear of production of resistant strains. If oseltamivir is instituted within 48 h of onset of illness, then it has a chance to reduce complications/disease severity along with illness duration. It is given in a dose of 75 mg twice daily for 5 days, which may be extended for 10 days in severe infections. Bioavailability of oseltamivir, administered through Ryles tube, in critically ill patients is comparable to that in uncomplicated H1N1 infected individuals. Higher doses of oseltamivir (150 mg twice a day for 10 days) may be used in seriously ill patients, influenza B strains, H5N1, resistant/reduced susceptibility strains of influenza A and infection at sites with reduced drug penetration (e.g., central nervous system). Even though, this regimen is safe and well tolerated, there is not much evidence in support of it. Besides, there are concerns regarding antiviral resistance with high dose oseltamivir. Treatment of oseltamivir resistant H5N1/H1N1 strains may be challenging. Intravenous zanamivir, inhaled laninamivir or combination antivirals such as oseltamivir-zanamivir and NAI-ribavirin-favipiravir may be utilized for treating resistant influenza. Low dose corticosteroids have been used in septic shock due to severe influenza and SARS/VZV pneumonitis so as to decrease the inflammatory tissue injuries. However, its use may lead to slower clearance of viral particles, increased rates of nosocomial infectious complications and mortality. Beneficial role of plasma and hyperimmune globulins in severe avian influenza (H5N1) and swine flu (H1N1) has been suggested by few case control studies and randomized controlled trials. However, the most potent intervention is to vaccinate the elderlies and the high risk individuals against seasonal influenza with the available vaccines.

(b) RSV—Aerosolized ribavirin is recommended only for immunosuppressed and children. Corticosteroids and immunotherapy may be combined along with ribavirin. Intramuscular palivizumab may be considered as prophylaxis in high risk patients.

(c) Management of SARS-CoV-2—The spectrum of illness secondary to SARS-CoV-2 ranges from a mild uncomplicated illness to severe pneumonia with ARDS with multiorgan failure and shock.

The treatment strategies are still evolving. The treatment of uncomplicated illness and mild pneumonia (without risk factors) is by enlarge supportive and
entails home isolation, symptomatic care, educating preventive measures and coming back to hospital if warning symptoms develop. Various antiviral agents are being used including hydroxychloroquine, remdesivir and convalescent plasma, beside others. It is important to initiate antiviral agents in moderate disease (RR > 24/min, SpO2 < 93%) rather than late in the course in severe disease. Oxygen support with face mask or HFNO should be given as per respiratory status and intubation to be done when it fails or work of breathing increases substantially. Anticoagulation is to be given in moderate and severe disease in prophylactic and high prophylactic dose respectively. RECOVERY trial has shown substantial mortality benefits in patients on oxygen or mechanical ventilation. Immunomodulators like tocilizumab and itolizumab are being tried in the cytokine storm phase when the disease is worsening despite use of corticosteroids.

(d) MERS-CoV—Treatment is largely supportive with no specific antivirals. Animal studies support the use of ribavirin and interferon 2a; however, similar advantage has not been observed in small observational human studies.

(e) VZV pneumonia—Acyclovir may be efficacious if utilized early in the course of infection.

(f) Parainfluenza virus—Aerosolized ribavirin for immunosuppressed patients only, not to be used in immunocompetent patients.

(g) Human Metapneumovirus—Treatment is largely supportive with no specific antivirals. Aerosolized ribavirin may be utilized only for immunosuppressed patients. The efficacy and safety of ribavirin in humans are not well established.

(h) Adenovirus—Treatment is largely supportive, with antivirals only for immunosuppressed patients and those with severe infections. Small case reports and non-randomized studies support the use of cidofovir in immunosuppressed patients. Immunosuppressed individuals may need preemptive cidofovir therapy based on weekly virological surveillance. Pooled IVIg may be used as complementary therapy as it has neutralizing antibodies against adenovirus. Ganciclovir and lipid ester derivatives of cidofovir are under evaluation for efficacy against adenovirus.

(i) Rhinovirus—Intranasal interferon (IFN) a-2b is useful for decreasing the symptoms and in primary prevention of rhinovirus infections. Further role in treatment of critically ill patients with severe rhinovirus infections is still not clear.

(j) CMV—The drugs available to treat CMV infections include ganciclovir, valganciclovir, acyclovir, valacyclovir, maribavir, foscarnet, and cidofovir. These drugs have been used prophylactically, preemptively or when the critically ill patients demonstrate CMV viremia. All these management strategies aim to start the therapy early so as to avoid development of end organ disease. Therapy is started universally in preventive strategy in comparison to preemptive therapy, where it is started only in high risk patients. The treatment should be started in immunosuppressed individuals, who may have severe manifestations of disease, and in patients with end organ involvement attributable to CMV infection. Severe CMV-CAP is one such example where treatment is required in immunocompromised patients or in severe pneumonia associated with hypoxemia in
immunocompetent patients. Important side effects of the antivirals used in managing CMV infections include bone marrow suppression and teratogenicity. Though there is enough evidence to not advise CMV therapy in immunocompetent patients, the experts feel that the same may not be held for critically ill immunocompetent patients. As against a complete course of antivirals in immunocompromised patients, only a limited duration of therapy may be required in immunocompetent patients just enough to bear the crisis of the acute phase. Pending convincing evidence, the experts advice that critically ill patients should be subjected to a clinical evaluation and those with high risk factors to acquire CMV infection should be offered treatment. Even though such an approach met with success in animal studies, only a handful of human studies have shown a decrease in rates of CMV infection and its sequelae. Well-designed trials are needed to draw conclusions on the role of periodic viral load monitoring to trigger antiviral therapy in critically ill immunocompetent patients. The dose of intravenous ganciclovir for CMV therapy is 5 mg/kg 12 hourly for the duration of infection. The oral equivalent of ganciclovir is valganciclovir which may be given for the entire duration with the same efficacy or may be started after the initial intravenous ganciclovir to complete the entire course of therapy. The dose of valganciclovir is 900 mg 12 hourly, to be given for 21 days. As discussed previously, immunocompetent individuals may not require the complete course as they may become better after receiving therapy for 1–2 weeks. The experts opine that the antiviral may be continued for an additional 1 week after the patient shows improvement in order to prevent a relapse. Foscarnet is an additional option, but it may not be preferred because of its nephrotoxicity. Foscarnet may be recommended in Ganciclovir resistant CMV.

(k) HSV—Acyclovir and valacyclovir have been used in patients with HSV related bronchopneumonitis or ARDS because of their good pulmonary bioavailability. However, the evidence of their safety and efficacy has been provided only by case reports or cohort studies. Studies have shown that even though acyclovir had the ability of restraining activation of herpes virus in ARDS patients, it did not have any additional benefit of decreasing duration of mechanical ventilation or mortality rates in immunocompetent patients with HSV bronchopneumonitis or ARDS.

(l) Role of corticosteroids—Corticosteroids have been used in influenza, SARS and VZV pneumonitis in order to decrease damage induced by inflammation in severe pneumonia. Dexamethasone is being currently used with evidence of benefit in COVID-19.

(m) Role of immunotherapies—Among the immunotherapies palivizumab, IVIg, plasma exchange and combination ganciclovir-CMV immunoglobulins have been approved for high risk pediatric RSV infection, influenza, GBS, and CMV pneumonitis, respectively.

### Specific Therapy for EBV Reactivation

There are no specific therapies, corticosteroids may be considered in the presence of hemolysis, thrombocytopenia or significant neurological involvement.
15.6.2.3 Specific Therapy for ARDS
Management of ARDS is largely supportive with oxygen support, protective ventilatory strategies, broad spectrum antibiotics, and antibiotic coverage for atypical organisms forming the backbone of support. Specific therapies may have a role to play in certain viral etiologies. For instance, ganciclovir and oseltamivir have been considered for CMV related ARDS and influenza, respectively. No specific treatment is available for MERS and SARS, however, ribavirin has been utilized without much promising results. Acyclovir has been used in HSV related ARDS with no advantages in terms of improvement of respiratory failure, mortality or duration of ventilation when compared with controls. Even though there is no concrete supportive evidence for acyclovir, it may be advisable to consider it as a therapeutic option in ARDS patients with HSV tracheobronchitis.

15.6.2.4 Specific Therapy for Viral Encephalitis
High dose intravenous acyclovir for at least 2–3 weeks is the backbone of management for herpes and varicella encephalitis. Early administration of acyclovir reduces mortality and ensuing cognitive deficits. Longer duration of antivirals may be required in immunosuppressed patients. Combination of foscarnet and ganciclovir, foscarnet alone, and pleconaril (inhibitor of viral replication) are indicated in CMV, HHV6, and enteroviral encephalitis, respectively. Corticosteroid use is not routinely advocated and they should be utilized only if associated with cerebral edema such as in postinfectious encephalitis. Experts also advice to use steroids in VZV encephalitis in order to prevent inflammatory vasculopathy. Intravenous immunoglobulins or plasma exchange may be tried in the setting of postinfectious encephalitis after the failure of steroids.

15.6.2.5 Specific Therapy for Myocarditis
Corticosteroids have been used in certain studies, however, meta-analysis have found that the use is controversial as they do not reduce mortality. A systematic review after evaluating the available evidence concluded that intravenous immunoglobulin (IVIg) cannot be recommended in viral myocarditis.

15.6.2.6 Specific Therapy for Viral Hemorrhagic Fever
Management of viral hemorrhagic fever is largely supportive. The pillars of therapy are maintenance of intravascular volume and electrolytes with appropriate intravenous/oral fluids, management of hypotension with vasopressors/inotropes, management of bleeding with transfusion of appropriate blood products, and avoidance of medications like aspirin, nonsteroidal anti-inflammatory drugs and intramuscular injections. Secondary bacterial infections should be diagnosed at the earliest and managed with appropriate antimicrobials. Ribavirin is indicated to treat Crimean–Congo hemorrhagic fever with a bolus of 30 mg/kg followed by 15 mg/kg for 4 days and then 7.5 mg/kg for 6 days. Vaccination is effective against Kyasanur forest disease.
Suggested Readings

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