Management of severe viral infections in the pediatric intensive care unit

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Abstract. Viral infections are major causes of morbidity and mortality among children worldwide. All children, regardless of geographic region, socio-economic status, or age, are vulnerable to severe viral infections. They often require specialized care that ideally necessitates admission to an intensive care unit. This article will review the major viral syndromes and pathogens that affect children, focusing on the current evidence for their acute management in the intensive care unit.

Keywords: Bronchiolitis, encephalitis, intensive care, pediatric, pneumonia, virus

1. Introduction

Viruses are the most important cause of infectious disease morbidity and mortality worldwide. There are numerous distinct clinical syndromes caused by individual viral species, with new viruses still being discovered. Viruses can infect nearly every human tissue and may directly or indirectly cause significant tissue damage, organ impairment and critical illness. Many viruses are closely related and, as a consequence, there is considerable overlap in viral clinical syndromes. Thus, in most cases, the exact viral identification is of less practical importance than promptly recognizing the associated clinical syndrome.

This article will focus upon the groups of viruses that cause severe disease in children, such as bronchiolitis/pneumonia, croup, encephalitis, febrile rash, and hemorrhagic fever. Therapies specific for the crit-

ical care management of these major viral syndromes in children worldwide and in settings with varying resources will be discussed. Influenza and viral infections in immunocompromised individuals, including human immunodeficiency virus, will be discussed in other articles in this issue.

2. Pathophysiology of viral infections

The virus-host interaction starts with entry of the virus into host target tissues. There are numerous portals of entry, depending on the nature and transmission characteristics of the virus. Viruses can be present in respiratory droplets or aerosols, in feces-contaminated food or water, or in body fluids such as blood, saliva, urine, or transplanted organs. The virus typically replicates and spreads either locally or systemically, depending upon its predilection for specific tissues. Some viruses will remain within the respiratory tract, while others will disseminate to numerous tissues and organs. While most infections occur in naive hosts, reactivation of latent virus is common in critically ill

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patients, especially in immunosuppressed individuals and the elderly. Tissue damage occurs either through direct damage or by inciting an immune response from the host, leading to a clinical syndrome that usually manifests with multiple systemic signs and symptoms.

3. Specific viral syndromes (Table 1)

3.1. Bronchiolitis/pneumonia

Bronchiolitis is the most frequent respiratory disease in children under the age of 2 yr worldwide. It typically occurs in winter months and is associated with fever, coryza, and progressive respiratory symptoms, including cough, tachypnea, and wheezing. The major inciting pathogens in children include respiratory syncytial virus, human metapneumovirus, coronavirus, rhinovirus, parainfluenza virus, and influenza virus, with many other potential etiologies [1–4]. The diagnosis is based on characteristic clinical features, with viral detection from respiratory secretions supportive of specific etiologies.

3.1.1. Predictors of outcome

Common risk factors for intensive care admission include prematurity, significant co-morbid disease and age less than 2 mo [5–7]. The presence of significant hypoxia (oxygen saturations <90%) and substantial work-of-breathing at presentation are also predictors of the need for intensive care support [8].

3.1.2. Therapy

Therapy for bronchiolitis is primarily supportive, as no specific anti-viral therapy has been shown to improve clinical outcomes. However, ensuring adequate nutrition and respiratory support is crucial for a good outcome. The use of non-invasive forms of ventilation, either through high-flow nasal cannula continuous positive airway pressure, or bi-phasic pos-

itive airway pressure may decrease the frequency of invasive ventilation requirements in bronchiolitis, although further high-quality studies are required [9–12]. High flow nasal cannula and continuous positive airway pressure are appealing options, especially in resource-limited areas where invasive ventilation is scarce. Invasive ventilation is required with profound hypercapnia, apnea, or worsening respiratory effort. Conventional ventilator strategies would include targeting lower tidal volumes of 5–7 mL/kg with permissive hypercapnia, avoidance of intrinsic positive-end-expiratory pressure with low rates and prolonged expiratory phases, and targeting oxygen saturations of greater than 90% [13]. Non-conventional modes of ventilation are required in a small proportion of children for ongoing air leak or a progressive inability to maintain adequate oxygenation, with both high-frequency oscillatory ventilation and high-frequency percussive ventilation having been studied with encouraging results [14, 15]. The typical duration of ventilator support is between five and seven days [16].

Randomized controlled trials of corticosteroids of various dosing regimes have reported no benefit in critically ill children, and are therefore not recommended [17, 18]. Moreover, bronchodilators such as albuterol or epinephrine are used widely despite no evidence in improving major critical care outcomes such as length of stay or mortality [19, 20]. Data regarding physiologic improvement after bronchodilator administration is conflicting, and hence, their routine use is not recommended in children without a previous history of wheezing or asthma [21–23]. Other therapies that have been studied and have minimal beneficial effect in critically ill children, include heliox; inhaled hypertonic saline, which may prevent hospitalization, but may not be effective in the critically ill child with bronchiolitis; and intra-tracheal administration of surfactant, which has only been minimally studied and carries significant costs [24–27]. Long-term outcomes are typically good

Table 1
Major viral pathogens for the severe viral syndromes of children

	Bronchiolitis/pneumonia	Croup	Encephalitis	Febrile rash	Hemorrhagic fever
Major pathogens	Respiratory syncytial virus	Parainfluenza	Herpes simplex	Measles	Dengue
	Human metapneumovirus	Corona virus	Enteroviruses	Varicella	Lassa
	Coronavirus	Measles	Influenza	Herpes simplex virus	Ebola
	Rhinovirus	Rhinoviruses	Arboviruses	Dengue	Marburg
	Parainfluenza				Yellow fever
	Influenza				

in the previously healthy child, although there is an association between early respiratory syncytial virus infection and childhood asthma [28].

3.2. Viral pneumonia

The etiological agent in viral pneumonia depends on the host's age. In the neonate, herpes simplex virus is the most common viral cause of pneumonia. Adenovirus and enterovirus are infrequent causes of neonatal viral pneumonia. In the infant, viral pneumonia has many overlapping features with bronchiolitis, with similar viral pathogens and often a more severe course. Additionally, new and emerging infections, such as Middle Eastern Respiratory Syndrome, and new influenza species will continue to be major etiologies [29, 30].

Management of the pediatric patient with viral pneumonia is typically supportive and similar to that outlined for viral bronchiolitis. The incidence of bacterial pathogen isolation from respiratory secretions in intubated children with viral pneumonia is greater than 50%, with higher mortality documented in children co-infected with influenza and methicillin resistant *Staphylococcus aureus* [4, 31, 32]. Vaccination against pneumococcus substantially reduces the incidence of viral pneumonia, implicating a major role for bacteria in the pathogenesis of viral pneumonia [34]. The role for empiric antibacterial treatment for pediatric viral pneumonia is unclear, and needs to be individualized depending on the clinical scenario and associated microbiologic testing [35].

3.2.1. Adenovirus pneumonia

Adenovirus pneumonia in children is unique in that it often results in severe acute disease as well as chronic lung damage manifested as bronchiolitis obliterans. Respiratory symptoms are progressive over years, and are related to the intensity of the initial adenovirus infection [36–38]. Adenoviral infections frequently also result in multi-system involvement with hepatitis, disseminated intravascular coagulation, and shock.

Initial management during the acute presentation of pneumonia may entail a prolonged period of mechanical ventilation, and frequently requires complex ventilation strategies. Standard protocols for lung protection, including minimizing tidal volumes delivered, limiting oxygen toxicity, and permissive hypercapnia should be instituted. The role of antiviral treatment in immunocompetent children with adenovirus pneu-

monia has not been studied, and hence no agent is currently approved for this indication. Cidofovir is effective against adenovirus *in vitro*, but has significant nephrotoxicity and no evidence of effectiveness, and is therefore not routinely recommended in the treatment of severe disease in immunocompetent children [39]. Ancillary measures such as ensuring adequate nutrition, aggressively treating bacterial co-infections, and allowing for viral clearance will optimize the chances at a good outcome. The role of extracorporeal membrane oxygenation support in these children has been associated with poor results [40]. All children with adenoviral pneumonia will require close follow-up upon hospital discharge, given ongoing supportive therapy requirements and the high risk of developing long-term respiratory disease.

3.3. Croup

Croup, or laryngotracheobronchitis, is a viral infection of the respiratory tract that produces subglottic inflammation and results in a classic syndrome of inspiratory stridor and dyspnea. It is an infection of childhood, typically occurring between ages 6 mo and 3 yr. The most common viral pathogen is parainfluenza, with a small subset due to rhinoviruses and bocavirus [41, 42]. Most children with croup do not require admission to intensive care; overall hospitalization rates have substantially declined over the past decades [43, 44].

Steroids, usually dexamethasone, reduce disease progression, although their role in severe disease is unclear [45, 46]. Inhaled epinephrine can transiently improve airway swelling and upper respiratory symptoms [47]. The role of heliox is undetermined and requires further study; however, the theoretical benefit of reducing airway resistance via decreasing the density and viscosity of the inhaled gas holds promise [48]. Its use is often limited by oxygen requirements, cost, and ensuring an adequate face seal of the delivery system, with low-flow nasal cannula being ineffective [25].

Progressive airway obstruction may necessitate airway intubation, which should be performed with an endotracheal tube size 0.5 to 1.0 mm below what would typically be used. Intubation should be anticipated and done by those with the most skill in a controlled environment, typically maintaining spontaneous ventilation with titrated doses of agents such as ketamine or inhalational anesthetics, where available. Once

intubated, these children will often have minimal lower respiratory tract disease and can typically be managed without significant ventilator support or large sedative requirements and able to play freely with a secured endotracheal tube. Extubation can be considered when there is an audible leak [49].

3.4. Viral encephalitis

Encephalitis is an inflammatory process of brain parenchyma associated with clinical signs of neurologic dysfunction. It is clinically manifested by an altered level of consciousness for more than 24 hr in the setting of at least one of the following: fever, seizures, focal neurologic findings, cerebrospinal fluid (CSF) pleocytosis, consistent electroencephalogram findings, or neuroimaging abnormalities [50].

Determining an infectious etiology for encephalitis is infrequent, with only approximately 16% of cases in California obtaining a confirmed etiology [51]. Encephalitis has a variety of infectious causes that are often sporadic and seasonal [52]. It is important to distinguish between acute encephalitis and post-infectious encephalitides, such as acute disseminated encephalomyelitis. These often have overlapping features, with historical, laboratory and imaging characteristics unique to each. Additionally, autoimmune encephalitis has become more frequent in recent years, although an underlying viral etiology is unclear [53]. Further, new and emerging infections causing viral encephalitis are not uncommon and are frequently undiagnosed.

Obtaining CSF in the critically ill child is often limited by suspicions of elevated intracranial pressure. In these situations, neuroimaging is the first step in the evaluation, ideally with a magnetic resonance imaging (MRI), if available. MRI will often detect inflammation within specific involved areas, suggesting etiologies. For instance, influenza encephalitis is often associated with a typical febrile syndrome and has a characteristic pattern of bilateral thalamic necrosis on MRI. If no MRI is available, then a computed tomography scan should be performed to rule out major abnormalities. However, the decision to obtain CSF with or without neuroimaging should be individualized, depending on the presence of focal neurologic signs, deep coma, or other clinical suggestions of elevated intra-cranial pressure. CSF findings are often non-specific, although microbiologic testing for bacterial and viral etiologies often dictates further management.

The major viral etiologies are contingent on age, season, and geographic location. The most common viral cause of encephalitis in the neonatal and infant population worldwide is herpes simplex virus [54]. Other major causes of childhood encephalitis are the other herpes viruses, namely varicella zoster virus, which typically produces a cerebellar syndrome; and those that typically affect immunocompromised individuals, such as cytomegalovirus, Epstein-Barr virus, and human herpes virus-6. Measles encephalitis is a major cause of morbidity in the developing world and will be discussed later.

Non-polio enteroviruses account for a large proportion of confirmed viral causes of encephalitis [50, 51]. Enterovirus peaks typically in the summer and fall, and more often presents with meningitis rather than encephalitis. In the neonate, enterovirus encephalitis is often associated with severe multi-system disease and carries mortality of above 10% [55, 56]. Specific enterovirus serotypes are associated with specific syndromes, some with greater disease frequency and severity than others, namely the coxsackie viruses, echovirus 18, and enterovirus 71, although serotype differentiation has very little clinical importance, given supportive management is the mainstay of therapy [57].

Arboviruses (arthropod-borne viruses) are becoming increasingly important across the world, especially during seasonal or regional epidemics of encephalitis where tick and mosquito populations are endemic. West Nile virus is the most common cause of epidemic viral encephalitis in the United States [58]. Neuroinvasive disease rarely occurs in children, with severe disease more likely to occur in the elderly. Symptoms are often non-specific, with associated movement disorders, weakness and/or paralysis, and cranial neuropathies. Chandipura virus has become more common in recent years in South Asia, characterized by a febrile prodrome progressing to acute encephalopathy [59]. Other major arboviruses that cause viral encephalitis include St. Louis encephalitis, Eastern Equine encephalitis, Western Equine encephalitis, and Japanese encephalitis (Table 2).

3.4.1. Management

HSV is treated with acyclovir, with cytomegalovirus and Epstein-Barr virus being effectively treated with ganciclovir. Influenza is treated with oseltamivir, although the evidence for its effectiveness in encephalitis is mixed. Management of viral encephalitis

Table 2
Geographic regions of major viral causes of encephalitis

Virus	Geographic region
California encephalitis group	Western United States
Chandipura	India
Eastern equine encephalitis	Americas
Japanese encephalitis	Southeast Asia, Australia
Murray valley encephalitis	Australia, New Guinea
Nipah virus	Southeast Asia
Rift-valley fever	Sub-Saharan Africa, Middle East
St. Louis encephalitis	Americas
West Nile virus	Worldwide

requiring critical care is primarily supportive. Seizures are frequent and should be treated aggressively with anti-epileptics such as phenytoin or phenobarbital, with continuous electroencephalographic monitoring where available [60]. Empiric therapy for cerebral edema with hyperosmolar agents such as mannitol and 3% saline has been used, although prospective efficacy data is lacking. The role of intracranial pressure monitoring is unclear, and which patients require targeted intracranial pressure or cerebral perfusion pressure targeted therapy deserves further study. Randomized controlled trials have shown improved mortality with cerebral perfusion pressure guided therapy in comatose children with bacterial meningitis, with less convincing improvements in viral encephalitis, as compared with intracranial-pressure guided therapy [61]. Depending on the suspicion for bacterial infection, antibacterial therapy should be started pending CSF findings and discontinued when a bacterial etiology is ruled out. Additional aggressive neuro-critical care measures, ensuring adequate sedation, temperature control, and correcting metabolic derangements are vital for improving the long-term outcomes.

The prognosis for the viral encephalitides in children is dependent on the infectious etiology and host factors. Eastern Equine encephalitis and Japanese encephalitis, for example, are often fatal or result in significant long-term morbidity, while other causes often improve with time and aggressive antiviral treatment. Neonatal encephalitis, regardless of viral cause, typically has long-term neurologic sequelae.

3.5. Rabies

Rabies encephalitis is a unique syndrome caused by the rabies virus that is most often transmitted by the

bite of an infected mammal. There are numerous effective protocols for pre- and post-exposure prophylaxis. Rabies disease has a classic syndrome of autonomic instability, fever, and progressive encephalopathy that is associated with significant morbidity and a high mortality. Hospital management of established disease has typically focused upon symptom control and palliation. However, there have been recent reports of survivors of rabies encephalitis through an intensive and prolonged critical care protocol involving sedation, nutritional supplementation, calcium channel blockade, focused neuroprotection, and avoidance of passive or active immunization [62]. However, significant long-term morbidity exists even with stringent adherence to the protocol [63–66]. The decision whether to implement this protocol for affected patients must take into account a variety of factors such as resource availability and family wishes.

3.6. Febrile rash

The constellation of findings in children with acute onset of fever and associated rash are various, with many viruses producing characteristic cutaneous patterns. Many are benign and resolve undiagnosed with minimal supportive therapy, although they often carry significant risks of nosocomial transmission requiring stringent infection control strategies. Notable syndromes that may lead to critical illness are discussed below.

3.6.1. Measles

Measles infection is caused by the rubeola virus and has a worldwide distribution. It is typically seen in childhood, is highly contagious, and effective vaccines are available. Severe measles still causes approximately 130,000 annual deaths in regions of the world without access to effective mass vaccination programs, primarily among children [67].

The majority of measles infections are only mildly symptomatic, producing the characteristic spreading rash. However, severe disease with complications requiring intensive care admission can occur in approximately 5% of hospitalized children, primarily with pneumonia progressing to acute respiratory distress syndrome, with frequent co-infection with bacterial pathogens [68, 69]. Measles encephalitis occurs in about one in 2000 cases and can manifest as acute and progressive, delayed autoimmune, or sub-acute sclerosing panencephalitis many years after the

initial infection, all of which carry long-term risks of morbidity and mortality.

Treatment consists of respiratory support, as well as anti-pyretics and ensuring adequate nutrition. Vitamin A is recommended in severe measles in regions where vitamin A deficiency is a concern, and should be considered in all regions regardless of nutritional status [70, 71]. Ribavirin is effective against measles *in vitro*, although limited clinical data exists about its safety and efficacy in humans with acute severe measles [72, 73]. In severe measles, antibiotics should be administered if there is a suspicion of bacterial co-infection [74].

3.6.2. Varicella

Varicella infection, a herpes virus transmitted by direct contact or airborne droplets, is also typically mildly symptomatic in most children, apart from the vesicular rash. Infrequently, complications may develop, such as pneumonia, encephalitis, and disseminated disease in immunocompromised individuals. Super-infection with Group A streptococcus produces sepsis, toxic shock syndrome, or necrotizing fasciitis and early appropriate therapy should be given [75, 76].

Pneumonia, typically developing a few days after appearance of the rash, is rare in children, more commonly presenting in adulthood. It typically has diffuse infiltrates on chest X-ray with ill-defined nodules progressing to calcifications. Treatment is with acyclovir as with all severe varicella infections, and adjunctive corticosteroids can be considered, although data is lacking [77].

3.6.3. Herpes simplex virus

Herpes simplex virus can cause a variety of diseases in the pediatric population. In neonates, it has three typical presentations: disease limited to the skin, eyes, and mucosa; central nervous system disease with encephalitis; or disseminated disease, which is rapidly progressive and often fatal. Infants and older children can present with herpes encephalitis or pneumonia. Because of the severity of illness, early empiric therapy with acyclovir is recommended when clinically suspected while awaiting confirmatory diagnostic testing. Testing consists of molecular analysis of suspected tissues, including mucosal swabs and CSF samples for the presence of virus; however, false negatives are known to occur early in disease course [78].

3.7. Hemorrhagic fevers

3.7.1. Dengue fever

Dengue fever is an acute disease caused by the flavivirus dengue and transmitted principally by the *Aedes aegypti* mosquito. It produces disease of variable severity dependent upon age, host factors, and virus type, with a wide spectrum of manifestations, ranging from asymptomatic to non-specific fever to severe disease with shock and hemorrhagic complications. Its geographic range is ever-changing (Fig. 1) given global migration and shifting weather patterns, with tropical, urban areas being at highest risk [79, 80]. It has a seasonal distribution, with summer being the peak period in most endemic areas, although transmission can be year-round.

Most patients with uncomplicated infection can be managed as an outpatient or on a routine hospital ward. The indications for admission to a critical care unit are the presence of severe disease, which is defined by dengue virus infection plus one of the following: plasma leakage resulting in shock or respiratory distress, severe bleeding, or severe organ involvement defined as elevations in aspartate aminotransferase or alanine aminotransferase, impaired consciousness, or myocardial dysfunction (Table 3). Prior criteria labeling dengue hemorrhagic fever as a separate entity have fallen out of favor due to significant misclassification [81].

Severe dengue may be associated with a variety of systemic complications, including acute respiratory distress syndrome, abdominal compartment syndrome, and severe hepatic dysfunction [82]. Patients should be closely monitored for disease progression, including serial hematocrit measurements and daily platelet counts.

The mortality rates for dengue virus infection should be less than 1% with timely recognition, triage, and treatment, with the majority of cases improving within hours of presentation [83]. There is no specific antiviral available currently, and there is no role for steroid administration [83, 84]. Treatment of severe dengue infection consists of two primary tenets: prompt fluid resuscitation and correcting any coagulopathy.

Crystalloid solutions, with Ringer's lactate having been the most extensively studied, are the resuscitation fluids of choice (Fig. 2), with colloids such as starch or dextran being associated with adverse events, and minimal data available on albumin administration [85]. The volume of crystalloid will depend on disease

Fig. 1. Global map of dengue infection.

Table 3
World Health Organization dengue case definitions

Dengue without warning signs	Dengue with warning signs	Severe dengue
<i>Fever and two of:</i> Nausea, vomiting	<i>Dengue with any of:</i> Abdominal pain	<i>Dengue with any of:</i> Severe plasma leakage leading to shock or respiratory distress
Rash	Persistent vomiting	Severe bleeding
Aches/pains	Fluid accumulation (ascites, pleural fluid)	Severe organ involvement: – Aspartate aminotransferase/alanine aminotransferase >1000 IU/L – Impaired consciousness – Heart failure
Leukopenia	Mucosal bleeding	
Positive tourniquet test	Lethargy, restlessness	
	Liver enlargement	
	Increase in hematocrit and decrease in platelet count	

severity, but should be judicious, typically starting with 10–20 mL/kg boluses, and with less volume required compared with bacterial septic shock. Fluid overload is a frequent occurrence, and fluid administration should be carefully titrated by serial hematocrit measurements and close monitoring of urine output and hemodynamic status. Diuretic administration should be considered early after initial resuscitation [86, 87]. Hemodynamic support with inotropes or vasopressors is sometimes required for cardiovascular support after ensuring adequate intravascular fluid volume repletion.

Bleeding should be quickly recognized and aggressively managed with blood product administration;

a lack of response to fluid resuscitation or an abnormally maintained or low hematocrit are typical warning signs of significant and ongoing bleeding. Platelet transfusions do not prevent hemorrhage in patients with thrombocytopenia and are necessary only if there is associated hemorrhage [88]. Packed red blood cells are necessary if there are signs of ongoing hemorrhagic shock. Cryoprecipitate or fresh frozen plasma may also be useful in preventing or stopping hemorrhagic complications. The majority of patients with severe dengue will require some blood product transfusion during their illness [89, 90].

Fig. 2. Algorithmic management of hemodynamics in severe dengue infection with shock.

3.7.2. Other hemorrhagic fevers

The central tenet of management of the viral hemorrhagic fevers is the management of the capillary leak, coagulopathy, and dehydration that will lead to the syndrome of bleeding, renal failure and hemoconcentration. These pathophysiological derangements can often progress to hemodynamic instability, worsening shock, and neurologic dysfunction, requiring aggressive supportive management. Specific treatment protocols are lacking, and care paths must be individualized depending on the clinical scenario and resources available.

Lassa fever is primarily endemic in Western Africa, where it causes 100,000–300,000 infections annually, with crude estimates of approximately 5,000 annual deaths. Its spread is via aerosolized rodent feces, and its incubation period is approximately one to three wk. It presents with fever, myalgias, hearing loss and bone pains, with progression to capillary leak, coagulation defects, shock and coma. Management consists of prompt administration of intravenous ribavirin, in addition to supportive care [91, 92]. Strict infection control to diminish the risk of nosocomial transmission is necessary [93, 94].

Ebola and Marburg viruses occur in Sub-Saharan Africa, with an undetermined exact mode of trans-

mission, although human-human transmission is well documented [95, 96]. These viruses have similar clinical manifestations, including fever and generalized malaise that progress over a few days to stupor, shock, and protracted bleeding, associated with leukopenia and transaminitis, with case fatalities approaching 90% [96–100]. Specific antivirals are not available. Infection control protocols must be strictly adhered to, given the high rates of nosocomial transmission [95, 97, 101].

Hantaviruses can cause severe hemorrhagic fever with renal syndrome, specifically in eastern Asia and Europe. This presents with severe fever and shock, progressing to renal insufficiency and bleeding, with a case-fatality rate of about 1%, typically recovering over a course of week [102]. An additional syndrome caused by hantaviruses present in the Americas is hantavirus cardiopulmonary syndrome. Starting with fever and myalgias, it can rapidly progress over the course of days to severe pulmonary capillary leak, progressive hypoxia, and shock. Upon diagnosis, affected patients should be triaged to higher levels of care at the earliest possible opportunity, given the rapidity of disease progression. It is often self-limited, requiring substantial supportive care during this cardiopulmonary phase, typically lasting two-five days, and is relatively rare in children. Ribavirin is effective *in vitro* and has proven

efficacious for hemorrhagic fever with renal syndrome, although data are lacking for cardiopulmonary syndrome [103]. Given the self-limited course of illness, extracorporeal membrane oxygenation for refractory respiratory failure and/or hemodynamic support has been effectively used in centers where it is routinely available [104, 105].

Yellow fever occurs in Sub-Saharan Africa, South America and the Caribbean, and has a case-fatality rate of approximately 10% in infants that present to care. It consists of fever, malaise, and transaminitis, which progresses, in a subset of patients, to multi-organ failure, including hepatic dysfunction, renal dysfunction, coagulopathy, and progressive coma. Recommendations for critical care management have been proposed, including nutrition, hemodynamic support, oxygen, coagulopathy correction, and dialysis [106].

Other viral hemorrhagic fevers include Rift Valley fever and Crimean-Congo hemorrhagic fever, which have been reported in Sub-Saharan Africa and central Asia, respectively. Intravenous ribavirin has demonstrated efficacy against Crimean-Congo hemorrhagic fever, although supportive therapy remains the cornerstone of management for both infections [107].

In conclusion, severe viral infections will continue to exert a major burden on pediatric critical care resources in both developed and developing countries, despite the presence of improved prevention schemes and better pathophysiologic understanding. There is little evidence on the targeted use of specific anti-viral therapies, and, in most cases, recommendations are based upon expert opinion. Given the burden of viral infections, significant work remains to better understand susceptibility and management of these major human pathogens including the development of targeted anti-viral therapies.

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