Cytokine Storm Syndrome Associated with Hemorrhagic Fever and Other Viruses

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Introduction

Cytokine storm syndrome (CSS) results from the failure to regulate appropriately the immune response with particular dysfunction of cytotoxic T cells and NK cells [1]. A potent trigger for activation of these cells is infection, and particularly viral infections, in subjects both with and without genetic mutations associated with primary HLH (pHLH) [2]. The most common viral infection triggering CSS is Epstein–Barr virus (EBV) and was the cause in 74% of children in whom an infectious agent was identified from a cohort of 219 with infection-associated CSS [3]. CSS associated with EBV and other herpes viruses are discussed elsewhere and the focus of this chapter will be other viruses, including hemorrhagic fever viruses [4]. In order to diagnose virus-associated HLH, presence of the pathogen should be confirmed by serology (paired acute and convalescent samples) or specific viral polymerase chain reaction (PCR) testing of blood or tissue. Other infectious or noninfectious causes of secondary HLH would also need to be excluded, although in cases of severe or life-threatening CSS prompt initiation of immunosuppressive / immunomodulatory treatment without delay is more important than determination of the underlying etiology.

Viral Hemorrhagic Fevers

The viral hemorrhagic fevers (VHFs) are caused by viruses belonging to one of five families: *Arenaviridae*, *Bunyaviridae*, *Filoviridae*, *Falviviridae*, and *Togaviridae* [5, 6]. They are all RNA viruses and require a nonhuman vertebrate or insect host to

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provide a natural reservoir. Initial infection occurs when humans come into contact with a host but subsequently human-to-human transmission of some of these viruses does occur. Typical presenting features include fever, dizziness, fatigue, muscle aches and weakness. Frequently VHFs occur as outbreaks or epidemics. The viruses and infections they cause are summarized in Table 1.

A systematic review of sHLH in zoonoses conducted in 2012 and covering studies published between 1950 and 2012 identified reports of HLH associated with Crimean-Congo hemorrhagic fever (CCHF) and hantaviruses [7]. Multiple cases of sHLH linked to dengue [8–39], Chikungunya [40], CCHF [41–43], hantavirus [44], and severe fever with thrombocytopenia syndrome (Bunyavirus) [45–47] have been described.

Dengue is a relatively common tropical infection [48] and may progress to more severe forms: dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). DHF is defined as dengue infection accompanied by fever lasting 2–7 days, hemorrhagic tendencies, thrombocytopenia and evidence of plasma leakage due to increased vascular permeability [49]. DSS is classified as DHF plus evidence of circulatory failure. The primary aspects of management are supportive with fluids and blood

Table 1 Viral hemorrhagic fever viruses and their associated diseases

Virus family	Host	Examples	Disease
Arenaviridae	Rodents—Spread through contact with excrement	Junin virus	Argentine hemorrhagic fever
		Lassa virus	Lassa fever
		Lujo virus	Lujo hemorrhagic fever
Bunyaviridae	Arthropods (ticks, mosquitoes, sand flies) and rodents	*Phlebovirus*—Rift valley fever virus	Rift valley fever
	Ticks	*Nairovirus*—Crimean-Congo hemorrhagic fever virus	Crimean-Congo hemorrhagic fever
	Rodents	*Hantavirus*—Hantaan virus Sin Nombre virus	Hemorrhagic fever with renal syndrome (HFRS) Hantavirus pulmonary syndrome (HPS)
Filoviridae	Fruit bats, *Rousettus* bats	Marburgvirus	Marburg hemorrhagic fever
	Fruit bats, primates	Ebolavirus	Ebola hemorrhagic fever
Flaviviridae	Mosquitoes	Yellow fever virus	Yellow fever
	Mosquitoes	Dengue virus	Dengue fever, dengue hemorrhagic fever
	Mosquitoes	Japanese encephalitis virus	Japanese encephalitis
	Mosquitoes	West Nile virus	West Nile fever
	Mosquitoes	Zika virus	Zika
	Ticks	Tick-borne encephalitis virus	Tick-borne encephalitis
Togaviridae		Chikungunya virus	Chikungunya

Adapted from [5, 6]

products as required [50]. Corticosteroids have been used; however, there has been uncertainty among clinicians about the efficacy and safety of corticosteroids in treatment of dengue with some considering them harmful [51]. An RCT of oral prednisolone (0.5 mg/kg or 2 mg/kg daily for 3 days) versus placebo, which included 225 patients with early dengue infection, found no prolongation of viremia or other adverse events in the steroid recipients [52]. It was not powered to assess efficacy; however, there appeared to be no reduction in the development of shock or other dengue-related complications. A Cochrane review published in 2014 which included 8 RCTs or quasi-randomized studies found the evidence to be of low or very low quality and insufficient to conclude whether corticosteroids are of benefit in dengue at an early stage or DSS [53]. Others, however, have suggested that the timing of steroids and patient selection may be critical [54]. A non-randomized retrospective study of adults with DSS with the most severe disease found those given a single dose of methylprednisolone (1 g intravenously) as a rescue treatment had a lower mortality (13%, 3/13 patients) than those not receiving steroids (47%, 15/32 patients) [55]. In these most severely affected cases it may be that patients had developed CSS.

Dengue has frequently been the trigger for HLH [56]. A large study in India of 212 patients with dengue identified 31 (14.6%) who developed CSS, including 23 with evidence of bone marrow hemophagocytosis [29]. In this group of 23 patients, 19 received IVIg and all recovered. Another study from Kolkata, India, reported 8 patients (2.2%) with HLH of 358 with dengue during the outbreak in 2012 [27]. The 8 cases received supportive therapy, blood component transfusions as required and parenteral dexamethasone (10 mg/m^2 in 3–4 divided doses/day) until hemodynamically stable before switching to oral tapering treatment for 21 days. IVIg (1 g/kg) was used in one patient as rescue therapy after failing to respond to 48 h of steroids. The patients with HLH were distinguished by persistence of fever for more than 7 days together with prolonged or progressive cytopenias, organomegaly, and sterile cultures. In a series of 33 children with HLH from Chennai, India, an infectious etiology was identified in 14 and specifically dengue in 5 [57].

Using a case-control design comparing patients with dengue who developed HLH (cases, $n = 22$) with patients with dengue without HLH (controls, $n = 88$), one study found cases had a younger age (median 1 vs. 13 years, $p < 0.01$), more frequent coinfection (18.2% vs. 4.5%, $p = 0.04$), and longer duration of fever (7 vs. 5 days, $p < 0.01$) [15]. Several studies have suggested testing for laboratory markers of HLH in cases of dengue, in particular ferritin, sCD163, and sCD25 [9, 10]. In a cohort of 208 patients with dengue, ferritin and sCD163 were significantly increased in patients with severe dengue. A report including patients with dengue during an outbreak on Aruba in the Caribbean found that levels of ferritin were significantly higher in patients with dengue compared with other febrile illnesses [58]. In another cohort of dengue-infected patients in Brazil, hyperferritinemia was associated with disease severity and a pro-inflammatory cytokine profile [58].

The features of severe dengue infection, as seen in dengue hemorrhagic fever or dengue shock syndrome, overlap with HLH suggesting a similar pathogenesis involving overactivation of the immune system leading to a hypercytokinemia [58, 59]. These features also seem to be shared in some cases of CCHF [41, 43]. One

reported a 14-year-old boy from Turkey with CCHF associated with leukopenia, thrombocytopenia, hypertriglyceridemia, hyperferritinemia and bone marrow hemophagocytosis. The pathogenesis of viral hemorrhagic fevers may overlap with CSS. A report of 5 patients with CCHF treated with high dose intravenous methylprednisolone (IVMP) suggested resolution of fever, increase in leukocyte and platelet counts and clinical improvement within 5 days of treatment [60]. Another study reported outcomes in 12 patients with CCHF treated with IVMP (up to 30 mg/kg/day), fresh frozen plasma (FFP), and intravenous immunoglobulin (IVIg) [61]. The treatment appeared to be successful with reduction of fever within 2 days, white cell count above 4500/μL in 4 days and platelets above 150,000/μL in 9 days. Finally, it has been suggested that Ebola outbreaks share many features of CSS [62–64].

While the VHFs represent an important group of viruses associated with CSS, a host of other viruses more commonly seen in North America and Europe can also trigger hemophagocytic syndromes.

Nonhemorrhagic Fever Viruses

A wide range of viruses other than those discussed above have been associated with CSS. These are summarized in Table 2 and reviewed in more detail below.

Influenza and Parainfluenza

CSS has been identified in association with seasonal influenza [65, 86–89], influenza A (H5N1, "avian flu") [90, 91], and pandemic influenza A (H1N1, 2009 "swine flu") infection [92–100]. In some cases, patients were immunocompromised or had additional risk factors such as leukemia [86, 97, 98], post-bone marrow transplantation for lymphoma [93], genetic predisposition [101], or cystic fibrosis [99]. However, CSS developed in previously healthy individuals following influenza H1N1 and H5N1 leading to death in both adults [95] and children [91, 100, 102]. A case of HLH following influenza vaccination in a patient with aplastic anemia undergoing allogeneic bone marrow transplantation has also been documented [103].

During the 2009 influenza H1N1 pandemic, a center in Germany conducted a prospective observational study of 25 critically ill patients with the infection [66]. All developed severe acute respiratory distress syndrome and hypoxemia and were mechanically ventilated. HLH was diagnosed based on the presence of three of four major criteria (fever, cytopenia, hepatitis, or splenomegaly) and at least one minor criterion (evidence of hemophagocytosis in bone marrow samples or increase in serum level of sIL-2Rα or ferritin, respectively). Nine (36%) of 25 patients met these criteria and eight (89%) of them died, compared with 4 (25%) of 16 patients without HLH. Six of the patients with HLH were treated (four with etoposide and dexamethasone, two with steroids alone) but the other three were moribund at the

Table 2 Nonhemorrhagic fever viruses associated with cytokine storm syndromes

Virus	Clinical associations	Outcomes	References
Influenza	Pneumonia, myocarditis, encephalitis, myositis	Mechanical ventilation, recovery	[65–67]
Parainfluenza	Croup, bronchiolitis, pneumonia	Recovery	[68]
Adenovirus	Upper respiratory tract infection, pneumonia, conjunctivitis, gastroenteritis, hepatitis, myocarditis, encephalitis	Recovery, more severe manifestations in immunocompromised hosts	[69, 70]
Parvovirus	"Slapped cheek syndrome"/ fifth disease, aplastic crisis, arthropathy, hepatitis, myocarditis	Recovery, pure red cell aplasia, chronic arthritis, hydrops fetalis, chronic fatigue syndrome	[71]
Hepatitis viruses	Hepatitis, arthritis, leukocytoclastic vasculitis	Recovery (hepatitis A), chronic hepatitis, cirrhosis, hepatocellular carcinoma	[72–74]
Measles	Interstitial pneumonia, encephalitis, thrombocytopenic purpura	Recovery, subacute sclerosing panencephalitis	[75–77]
Mumps	Parotitis, pancreatitis, orchitis, meningitis, encephalitis	Recovery, deafness, sterility rarely after orchitis	[78, 79]
Rubella	Arthralgia, arthritis, encephalitis, congenital rubella syndrome	Deafness, developmental delay, cardiovascular and ocular defects in congenital rubella syndrome	[80]
Enterovirus	Respiratory and gastrointestinal infections, pancreatitis, meningitis, encephalitis, neonatal sepsis,	Neurological impairment in some children after meningitis	[81]
Parechovirus	Sepsis-like illness, meningitis, encephalitis, hepatitis	Neurological sequelae in some young infants	[82, 83]
Rotavirus	Gastroenteritis, seizures, encephalopathy/encephalitis	Recovery, rarely intussusception	[84]
Human T-lymphotropic virus	Adult T cell leukemia/ lymphoma, demyelinating disease, autoimmune diseases	Tropical spastic paraparesis, systemic lupus erythematosus, Sjögren's syndrome	[85]

time of diagnosis with HLH and were not considered suitable for treatment. The study suggests that CSS/HLH may have been a significant contributor to multiorgan failure and death in critically ill patients during the influenza A H1N1 pandemic.

Reports have indicated that avian influenza A (H5N1) can lead to severe and widely disseminated infection outside the respiratory system. In one case, a previously healthy nine-year-old Vietnamese girl died following encephalitis and coma with virus detected in rectal swabs, serum and cerebrospinal fluid [102]. Hemophagocytosis was detected in bone marrow from several patients with H5N1

infection [90, 91, 104–106]. In vitro studies indicated that recombinant hemagglutinin (H5) from H5N1 influenza suppressed perforin expression and reduced cytotoxicity of human $CD8^+$ T cells to kill H5-bearing cells [107]. This failure of clearance of infected cells could promote lymphoproliferation and hypercytokinemia as seen in CSS. Another study measured cytokine levels in a familial group of patients with H5N1 influenza in Hong Kong and found particularly high serum concentrations of interferon induced protein-10 (also known as CXCL10) and monokine induced by interferon γ (CXCL9) [108]. Taken together with other in vitro work, the authors suggest this hypercytokinemia may contribute to pathogenesis in fatal influenza infection. How might these cases be treated?

Drawing parallels with EBV-associated HLH, Henter et al. proposed a modified HLH-94 treatment protocol for influenza A (H5N1)-associated HLH in addition to antiviral and supportive therapy [109, 110]. For children, they suggested intravenous etoposide 150 mg/m^2 once per week and dexamethasone initially 10 mg/m^2 once daily. They recommended reduced doses of both drugs in patients aged 15 years or older and advised against upfront use of cyclosporin A (CsA) in all cases due to the relative frequency of renal complications in H5N1 infection.

Influenza B has been suggested as the trigger for HLH in a 24-year-old man with systemic lupus erythematosus (SLE) [111]. Several weeks after his initial diagnosis of SLE when he presented with a pericardial effusion, he developed fever, erythematous rash, splenomegaly, hypertriglyceridemia, and ferritin of 95,703 ng/mL. Influenza virus B was detected in the patient's nasal lavage sample and no other infective triggers for HLH were apparent. His pericardial effusion recurred with progression to cardiac tamponade, and he was managed with ventilation and pericardiocentesis. His condition initially improved after steroid pulse treatment, but he was started on colchicine 1 mg/day after reaccumulation of the pericardial fluid. He remained stable on low-dose prednisolone and colchicine. The relative contributions of SLE and influenza infection to pathogenesis of CSS in this case are unclear. While many reports have associated influenza with HLH, parainfluenza has been documented once.

A case of CSS in a 33-year-old Chilean man characterized by fever, evanescent rash, hepatosplenomegaly, anemia, thrombocytopenia, hyperferritinemia, and hemophagocytosis on bone marrow biopsy was attributed to parainfluenza virus-2 infection detected by polymerase chain reaction (PCR) testing of respiratory and enteric samples [112]. He was treated with etoposide, dexamethasone, and CsA following the HLH-94 protocol, and he made a complete recovery remaining in remission after 2 years of follow-up.

Adenovirus

Adenovirus infections are frequent in childhood presenting with respiratory, gastrointestinal, or ocular manifestations [70]. These are usually mild in immunocompetent hosts but may lead to more severe disease including pneumonia, hepatitis, and encephalitis in the immunocompromised.

CSS has been described in adults and children secondary to adenovirus infection [113–124]. It has occurred in previously healthy children with the initial presentation of pneumonia [114, 115, 120]. One of the patients was treated with dexamethasone and CsA and the other two with IVIg, and all recovered. In a large single-center study of HLH in children under 1 year of age, three of four infants with adenovirus-associated HLH survived [116]. A case in an adult while receiving chemotherapy for a solid tumor has been reported [121]. A young child being treated with chemotherapy for Langerhans cell histiocytosis developed recurrent viral-associated HLH, in one instance caused by adenovirus [117]. Several cases of adenovirus-associated HLH have been reported post-hematopoietic stem cell transplantation [113], associated with sJIA [119], and in brothers with X-linked agammaglobulinemia [124].

Parvovirus

Parvovirus B19 is the cause of erythema infectiosum (fifth disease or "slapped cheek syndrome"), which is common in childhood [71]. In addition to a rash, adults more frequently develop arthralgia and myalgia.

CSS has been reported in adults and children in association with parvovirus B19 infection [125–132]. One report detailed five previously healthy adults whose disease resolved spontaneously [133]. In other cases, the most frequent underlying disease was hereditary spherocytosis [4, 128]. Cases of CSS triggered by parvovirus B19 in patients with another underlying condition have been reported: post-renal transplant [134], post kidney-pancreas transplant [135], B-cell acute lymphoblastic leukemia [136], autoimmune hemolytic anemia [137], Evans syndrome (autoimmune hemolytic anemia and autoimmune thrombocytopenia) [138], and pregnancy [139].

Coinfection with parvovirus B19 and another pathogen has been reported in association with HLH in several cases, including EBV [126, 140] and Klebsiella [141].

Among 28 cases of parvovirus-associated HLH, the majority were woman over 15 years of age, and 22 survived despite 16 of them having no specific treatment [142]. This suggests a better prognosis than other forms of viral-associated CSS [4], although fatalities and serious complications such as acute myocarditis have been reported [143, 144]. Case reports have detailed use of glucocorticoids, IVIg, CsA, and anakinra (IL-1 receptor antagonist) in treatment of parvovirus B19-associated HLH [145].

In some of the cases of HLH attributed to parvovirus B19, viral nucleic acid was detected in blood or tissues by PCR. It is known that virus may persist for weeks or months, and therefore detection of viral DNA in tissues does not definitively confirm acute infection [71]. The most reliable marker of this is detection of virus-specific IgM and a fourfold increase or seroconversion of IgG in paired serum samples. However, care should be taken in interpretation of serology samples in patients after treatment with IVIg.

Hepatitis Viruses

Various hepatitis viruses have been detected in association with CSS. Hepatitis A virus is the most-frequently reported [146–157]. Features of fulminant acute viral hepatitis may be similar to CSS. Hepatitis A-triggered MAS has been reported in several patients with underlying systemic JIA or Still disease [148, 154, 157]. Successful treatments for hepatitis A-triggered HLH have included glucocorticoids, IVIg [150, 156], and the HLH-2004 etoposide-based protocol [154]. In addition to hepatitis A, other hepatitis viruses have also been found to cause HLH.

Hepatitis B virus has been reported as a potential trigger for CSS [158, 159]. The first reported case did not respond to steroids, IVIg, or CsA, but the patient did respond to etoposide, although subsequently succumbed to fulminant infection [158]. A fatal case of CSS was reported in a patient with the combination of chronic active hepatitis B and acute hepatitis C infection despite intensive immunosuppressive (intravenous methylprednisolone, intravenous CsA, granulocyte-colony stimulating factor, IVIg, and anti-thymocyte globulin), and supportive treatment [160].

CSS was identified in a 60-year-old woman with chronic hepatitis C infection [161]. In this case, it was speculated whether the more acute triggers for development of sHLH were the interferon and ribavirin used as treatment for hepatitis C virus which were started 3 months before the characteristic features of CSS: fever, splenomegaly, coagulopathy, anemia, and thrombocytopenia.

Hepatitis E is typically a self-limited illness with average duration of 4–6 weeks and presenting with fever, nausea, vomiting, abdominal pain, anorexia, hepatomegaly, and jaundice [162]. CSS associated with hepatitis E infection has been reported in a small number of cases [163–165]. In one patient with rheumatoid arthritis, MAS developed within 24 h of her fourth tocilizumab infusion. Investigations for infections revealed positive serology, and hepatitis E virus RNA was detected in blood and stool by PCR [164]. In a second patient, sHLH appeared to be triggered by coinfection with hepatitis A and hepatitis E [165].

Measles, Mumps, and Rubella Viruses

CSS has occurred in a small number of cases following measles infection [18, 75, 76, 166]. In eight of the cases patients developed interstitial pneumonia. The reported therapies included supportive treatment alone, intravenous methylprednisolone, or the HLH-2004 protocol. One case of sHLH following measles vaccination has been reported in a 19-month-old girl who developed persistent fever, hepatosplenomegaly, pancytopenia, liver dysfunction, and hemophagocytosis 1 week after vaccination [167]. A second case of suspected sHLH was reported in a previously healthy 14-month-old girl following the combined measles, mumps and rubella (MMR) vaccination and the authors speculate whether there may have been an underlying genetic predisposition [168].

Mumps infection has rarely been associated with CSS [78, 169]. In one case from China, a previously healthy 21-year-old male had persistent painful parotid gland swelling for 30 days and fever for 15 days together with typical features of CSS, including hemophagocytic macrophage infiltration on bone marrow biopsy. Anti-mumps virus IgM was positive but testing for bacteria and other viruses in peripheral blood was negative. Although there was initial response to high doses of methylprednisolone, IVIg, and etoposide, he succumbed 4 weeks after admission. In the second case, a 39-year-old female with parotitis and acute pancreatitis followed by features of CSS achieved complete response with corticosteroids.

Rubella virus-associated HLH has been reported in patients with ages ranging from young infants to adults [170–173]. In one case of a 26-year-old woman, serology was positive for both varicella-zoster virus (VZV) IgM and rubella virus IgM suggesting dual infection.

Enterovirus

Enteroviruses, which include the Coxsackieviruses and echoviruses, can cause a wide range of clinical presentations from mild respiratory and gastrointestinal infections, and hand-foot-and-mouth disease, to more severe conditions such as pancreatitis, meningitis, encephalitis, and neonatal sepsis [81]. Over 10 cases of enterovirus-associated CSS have been reported in the literature [116, 174–181]. One case occurred in an adult infected with Coxsackie virus A9 [174]. However, a significant proportion were in neonates or infants [116, 175, 179–181]. A case of vertical transmission of Coxsackie virus B1 leading to HLH in a 4-day-old neonate was reported with virus isolated in the throat and stool, and exclusion of inherited disease with normal perforin and CD107a expression [180]. The baby was successfully treated with corticosteroids, CsA, and etoposide. A case of fatal HLH was described in a 4-month-old infant with liver dysfunction (AST 626 IU/L, ALT 121 IU/L), high ferritin (1100 ng/mL), and hemophagocytosis in a liver biopsy [176].

Parechovirus

Virus of the *Parechovirus* genus are within the family *Picornaviridae* and were previously considered to be within the *Enterovirus* genus [81]. Human parechovirus-3 (HPeV-3) in neonates and infants can manifest with a sepsis-like presentation, and one publication has reported young infants with fever, rash, leukopenia, thrombocytopenia, and hyperferritinemia [181]. This and other studies have suggested that HPeV-3 can cause an HLH-like illness, although the reason why other types of HPeV do not seem to cause a similar febrile illness is not clear [82].

Rotavirus

Rotavirus is one of the leading causes of infectious, dehydrating gastroenteritis in children globally with over 200,000 deaths reported annually [84]. CSS associated with rotavirus infection has been described in a small number of cases in the published literature [182–184]. In two of the cases there were significant underlying conditions. In the first, a 67-year-old man developed rotavirus enteritis 1 month after live-unrelated renal transplantation, and he developed fever, pancytopenia, altered consciousness, elevated liver enzymes, hypofibrinogenemia, and hyperferritinemia [182]. He also had herpes zoster infection and varicella zoster virus DNA was detected in his CSF. Bone marrow analysis confirmed hemophagocytosis, and he responded to acyclovir and pulsed methylprednisolone therapy. The second case was a 3-year-old child approximately 30 months after allogeneic hematopoietic stem cell transplantation for familial HLH [183]. She developed fever, diarrhea and lethargy, and she progressed to multiorgan failure meeting six of the HLH criteria on day 2 of admission. At this stage, rotavirus antigen was detected in stool and all other bacterial, viral, and fungal testing was negative. She received high dose corticosteroids and IVIg but developed invasive fungal infection and succumbed 4 weeks later.

Human T-Lymphotropic Virus

Human T-lymphotropic viruses (HTLVs) belong to the family of retroviruses. HTLV type-1 (HTLV-1) is associated with adult T cell leukemia/lymphoma, demyelinating disease, and autoimmune conditions [85]. A case has been reported of a woman who was a carrier of HTLV-1 who was diagnosed as having adult T-cell leukemia/lymphoma and B cell lymphoma-associated hemophagocytic syndrome [185]. HTLV type-3, the cause of AIDS, and its association with CSS is covered in a separate chapter in this textbook.

Conclusion

Viruses are the single most common infectious trigger for the final common pathway resulting in CSS. Identification of the pathogen usually requires serological or PCR testing, although caution is required in interpretation of these investigations in relation to the timing of the acute infection. In many of the reported cases, development of CSS appeared to be multifactorial involving more than a single infectious agent sometimes on a background of genetic predisposition, malignancy, immune suppression, or rheumatological disease. In the acute setting of life-threatening CSS, determining the etiology is subsidiary to management with multiorgan supportive therapy and high-dose glucocorticoids. Other than a modified HLH-94

treatment protocol for influenza A (H5N1)-associated HLH, there is no evidence from controlled trials for a particular treatment regime based on the triggering virus.

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E. S. Sen declares no competing interests.

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