Review

Emergency and Critical Care Medicine

OPEN

Research progress of viral sepsis: etiology, pathophysiology, diagnosis, and treatment

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Abstract

Sepsis is a common systemic disease characterized by various physiological and pathological disorders. It can result from infection by various pathogens, such as bacteria, viruses, and fungi. The rate of culture-negative sepsis is almost 42%, indicating that most patients may have nonbacterial infections. With the outbreak of coronavirus disease 2019, viral sepsis has attracted growing attention because many critically ill patients develop sepsis. Viral sepsis can be caused by viral infections and combined with, or secondary to, bacterial infections. Understanding the common types of viral sepsis and the main characteristics of its pathogenesis will be helpful for effective diagnosis and treatment, thereby reducing mortality. Early identification of the causative agent of viral sepsis can help reduce the overuse of broad-spectrum antibiotics. In this article, we reviewed the common viruses of sepsis, their potential pathophysiology, targets of diagnosis, and remedies for viral sepsis.

Keywords: Acute gastrointestinal injury, Acute kidney injury, Acute lung injury, Cytokine storm, Diagnosis, Treatment of viral sepsis, Viral sepsis

Introduction

Sepsis is a fatal organ malfunction caused by an abnormal host response to multiple infections.[1] There were 48.9 million cases of sepsis worldwide in 2017, with a morbidity rate of 677.5 cases per 100,000 people.[2] It is expected to cause approximately 11 million deaths worldwide.[3] Sepsis can result from infection by multiple pathogens, such as bacteria, viruses, and fungi. Several recent studies have focused on sepsis. However, there are few studies on viral sepsis, most of which have focused on bacterial sepsis.[4–6] In a study on the global epidemiology of severe pediatric sepsis, 54.4% of patients had bacterial infections, while viruses and fungi accounted for 21% and 13.4%, respectively.[7] Among 700 samples collected from children hospitalized with severe acute respiratory infection (SARI), 547 (78.1%) tested positive for viral infection.[8]

Because of the lack of a definition, diagnosis, and detection of viral sepsis, the reported proportion of viral infections among adults with sepsis is very low. Viral infections should be considered in patients who lack evidence of bacterial, parasitic, or fungal infections. A study found that 61% of patients admitted with viral sepsis were diagnosed with pure viral community-acquired pneumonia according to the Sepsis-3 criteria.[9] Viral sepsis can be caused by viral infections and combined with, or secondary to, bacterial infections. Influenza virus infections are often associated with *Streptococcus pneumoniae* and *Staphylococcus aureus*. The cytomegalovirus, Epstein-Barr virus, and other viruses may be reactivated after bacterial sepsis.[10]

Viral sepsis lacks specific clinical manifestations, particularly during the early stages. If sepsis is combined with respiratory or digestive tract symptoms, it can be easily misdiagnosed as a focal infection. Patients with viral sepsis may have focal positional symptoms or signs of infection during the early course of the disease. Studies have shown that the most common site of infection is the respiratory system, which accounts for 68.2% of infections.[11] The early symptoms in patients infected with the influenza virus are mainly in the respiratory tract, followed by acute respiratory distress syndrome.[12] Most patients with enterovirus infections experience show early gastrointestinal symptoms.[13] Dengue virus infection in its early stages is characterized by high fever, systemic muscle pain, and joint pain.[14] Clinical treatments are centered on identifying the pathogen that causes sepsis as soon as possible. Understanding the common types of viral sepsis and the main characteristics of its pathogenesis, clinical manifestations, and effective diagnostic and treatment strategies can improve patient prognosis. Early identification of the causative agents of viral sepsis can help reduce the overuse of broad-spectrum antibiotics. In this article, we review the common viruses of sepsis, their potential pathophysiology, targets of diagnosis, and remedies for viral sepsis.

The common viruses of viral sepsis

Influenza virus

The influenza virus is the most common pathogen that causes viral sepsis. Children younger than 5 years, pregnant women, immunosuppressed individuals, and older adults are at high risk for influenza. The incidence and mortality of influenza gradually increase with age in adults.[15] The influenza virus in the respiratory tract causes extensive damage to the airways and alveolar epithelial cells, which seriously affects gas exchange.[16] Severe infections can manifest as diffuse infiltration in lungs, refractory hypoxemia, and even acute respiratory distress syndrome.[17] A study on sepsis in infants reported that the detection rate of influenza virus was 7.8%.[18]

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Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Emergency and Critical Care Medicine (2024) 4:2

Received: 2 November 2022; Accepted: 7 March 2023

Published online: 25 April 2023

http://dx.doi.org/10.1097/EC9.0000000000000086

Respiratory syncytial virus

Respiratory syncytial virus (RSV) usually causes lower respiratory tract infections in children.[19] Premature children delivered by cesarean section, those with immune dysfunction, and those with bronchopulmonary dysplasia are at a high risk of RSV infection.[20] Respiratory syncytial virus infections mainly cause minor symptoms that manifest as bronchiolitis or viral pneumonia.[21] Respiratory syncytial virus–associated sepsis and septic shock are serious complications of RSV infection and usually occur in neonates with low immunity. The main manifestations include multiple systemic symptoms such as dyspnea, central apnea, status epilepticus, ventricular tachycardia, and myocarditis.[22]

Coronaviruses

Severe acute respiratory syndrome coronavirus 2 and Middle East respiratory syndrome coronavirus usually lead to an epidemic of serious respiratory syndromes among people, whereas human coronavirus NL63 (HCoV-NL63), HCoV-OC43, and HCoV-229E mainly cause infections in infants and the older people.[23] The number of patients with severe sepsis has increased with the outbreak of the novel coronavirus disease 2019 (COVID-19). The immune system of patients with severe COVID-19 is abnormally activated, showing typical characteristics of sepsis, such as cytokine storm, circulation disorder, weak pulse, severe lung injury, as well as liver, kidney, and other multiple organ dysfunctions. A meta-analysis showed that the prevalence of COVID-19–related sepsis was 77.9%, and acute respiratory distress syndrome (ARDS) was the most common clinical presentation.[24]

Adenoviruses

Adenoviruses are common DNA viruses that primarily infect the respiratory tract, digestive system, and conjunctiva. Severe patients present with hepatitis, gastroenteritis, myocarditis, pneumonia, pancreatitis, meningoencephalitis, hemorrhagic cystitis, and acute conjunctivitis.[25–27] Because of their low immunity, adenovirus infections are more common in young children.[28] One study reported 3 cases of fatal neonatal sepsis related to human adenovirus type 56.[29] Another study showed that 2 patients infected with human adenovirus C2 after allogeneic hematopoietic stem cell transplantation (allo-HSCT) developed bacterial septicemia.[30]

Other viruses

Enteroviruses usually cause mild symptoms; however, neonates are prone to serious complications and even sepsis.[31] Human parechoviruses (HPeVs) cause serious infections in neonates and young infants.[32] A study reported that the detection rates of HPeV-1 and enteroviruses in young infants diagnosed with sepsis were 5% and 38%, respectively.[33] Li et al. reported a case in which a young Chinese man was diagnosed with herpes simplex virus-associated sepsis using next-generation sequencing.[34] Rhinoviruses cause common viral infections of the upper respiratory tract that primarily cause flu-like illnesses.[35] Patients with premature birth, congenital heart disease, and noninfectious respiratory diseases are more likely to have severe symptoms. A recent study reported that a patient infected with human rhinovirus A45 had viral sepsis and central nervous system involvement.[36] Table 1 summarizes the susceptible populations and clinical manifestations of common viruses.

Pathophysiology of viral sepsis

Cytokine storm of viral sepsis

The specific pathogenesis of sepsis is unclear, but some consensus suggests that the balance between the systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome is disrupted in sepsis.[4] Cytokine storms are processes in which various tissues and cells (mainly immune cells) lose their negative feedback mechanisms to the immune system under the influence of external stimuli (such as viruses and bacteria) and oversecrete inflammatory cytokines. Viral infections can induce severe cytokine storms.[44]

Inflammatory cytokines are produced during the virus-activated innate immune response. Innate immunity is activated via pattern recognition receptors (PRRs). Pattern recognition receptors can recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[45] Common PRRs include toll-like receptors (TLRs), retinoic acid-induced gene 1, and NOD-like receptors (NLRs), which initiate innate immune responses.[46] Toll-like receptors are the most researched PRR and are expressed in various cellular compartments such as dendritic cells, neutrophils, macrophages, and T and B cells. Transmembrane proteins include TLR1, TLR2, TLR4, TLR5, TLR6, and TLR11.[47] Toll-like receptors recognize viral proteins and induce NF-κB activation through adaptor proteins such as myeloid differentiation protein 88 (MyD88), TIR receptor-inducing interferon-β (TRIF), TIR domain-containing adaptor protein, and TRIF-related adaptor molecule (TRAM).[48] Activated NF-κB promotes the production of inflammatory cytokines. NOD-like receptors are intracellular receptors that recognize PAMPs and DAMPs. NOD-like receptor family pyrin domain-containing proteins, which consist of NLR proteins, apoptosis-associated speck-like proteins, and pro-caspase-1, participate in inflammasome.[49] Activation of the NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasome is a widely researched medium that plays an essential role in both inflammatory and antiviral responses. The NLRP3 inflammasome participates in the activation of caspase-1 and the generation of interleukin-1β (IL-1β) and IL-18[50] (Fig. 1). Activated cytokines lead to systemic inflammation and multiple organ dysfunction. Acute lung injury (ALI), acute renal injury, and acute gastrointestinal injury (AGI) are common clinical manifestations (Fig. 2).

Lung injury in viral sepsis

The respiratory system is the most commonly infected system and the most common system to fail in sepsis.[51] Exposure of the respiratory tract to the environment increases the risk of viral infection. Viruses causing respiratory tract injury include influenza virus, coronavirus, and RSV.[52] Most patients with sepsis present with ALI and ARDS.[53] The interaction between multiple inflammatory cytokines is key to promoting the progression of lung injury. Interleukin 1β, IL-6, and tumor necrosis factor α (TNF-α) are considered as crucial proinflammatory mediators.[54] A study revealed that IL-1β suppression of vascular endothelial-cadherin transcription was the determining factor of endotoxemia-induced lung vascular injury.[55] Interleukin 5 can reduce lung injury by modulating the immune response and inhibiting sepsis-induced systemic inflammation.[56] Tumor necrosis factor α is involved in the early pathogenesis of sepsis induced ALI. Using TNF-α Ab prophylactically can decrease serum cytokines and lung myeloperoxidase activity.[57] Inflammatory factors directly damage the endothelium and increase vascular permeability. Studying the mechanism of injury and the biological function of cytokines in sepsis will provide a new strategy for the prevention and treatment of ALI.

Acute kidney injury in viral sepsis

Acute kidney injury (AKI) is characterized by a rapid decrease in renal function due to different causes. Sepsis-associated AKI refers to meeting the diagnostic criteria for both sepsis and AKI, excluding other causes that can explain AKI.[58] It was reported that

Table 1

Common Viruses Causing Sepsis

Virus	Susceptible Population	Clinical Manifestation	References
Influenza virus	Children younger than 5 y, pregnant women, old adults, immunosuppressed individuals	Influenza pneumonia, influenza sepsis, acute encephalitis, acute myocarditis, myositis and rhabdomyolysis	[10]
Respiratory syncytial virus	Infant, young children with preterm birth, cesarean section and bronchopulmonary dysplasia, immunocompromised children	Bronchiolitis, viral pneumonia, central apnea, status epilepticus, ventricular tachycardia, myocarditis	[21,22]
Coronaviruses	Infants and the elderly (human coronavirus NL63 [HCoV-NL63], HCoV-OC43, and HCoV-229E), all humans (SARS-CoV-2 and MERS-CoV)	Pneumonia, ARDS, thromboembolism and hypercoagulopathy, AKI, liver dysfunction, CNS dysfunction	[24,37,38]
Adenoviruses	Young children	Hepatitis, gastroenteritis, myocarditis, pneumonia, pancreatitis, meningoencephalitis, hemorrhagic, cystitis and acute conjunctivitis	[25–27]
Enteroviruses	Neonates, pregnant woman	Myocarditis, hepatitis, coagulopathy, meningoencephalitis, pneumonia	[39]
Human parechovirus	Neonates, young infants	Gastroenteritis, respiratory tract infections, fever, rash and severe irritability, encephalitis, seizures, acute flaccid paralysis	[32,40–43]

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CNS, central nervous system; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

approximately 60% of sepsis patients in the intensive care unit develop AKI.[59,60] The pathophysiology of sepsis-associated AKI is complex and has not been fully elucidated. Existing research has mainly focused on the following aspects: inadequate fluid resuscitation in sepsis, septic cardiomyopathy, microvascular dysfunction, and maladaptive redistribution of tissue blood flow may trigger ischemic renal injury.[61] Sepsis causes the release of PAMPS and DAMPS, which interact with PRR in immune, endothelial, and renal tubular epithelial cells. This process initiates downstream signaling cascades and triggers the release of many proinflammatory factors.[62,63] These inflammatory reactions eventually lead to damage to the tubular epithelial cells.

Gastrointestinal tract injury in viral sepsis

As a part of multiple-organ function disability syndrome, AGI is the most common symptom of critical patients and can be caused by a variety of factors. Gastrointestinal dysfunction is associated with a high mortality rate in patients with sepsis.[64] Another study showed that 86.7% of critically ill patients with COVID-19 had AGI.[65] The gastrointestinal tract is one of the earliest and most seriously affected organs in the pathogenesis of sepsis. Damage to the gastrointestinal mucosal barrier and intestinal microecology disorders can cause the displacement of intestinal bacteria and endotoxins and aggravate the condition of critical patients.[66] When AGI occurs in patients with sepsis, studies have confirmed that ghrelin levels and the serum gastrointestinal hormone motilin are significantly decreased, which affects gastrointestinal motility and means that harmful metabolites cannot be removed in time. These reactions further aggravate the damage to gastrointestinal function.[67]

Diagnosis

Because of the lack of specific clinical manifestations, viral sepsis is often difficult to detect in its early stages. The first step involved establishing a diagnosis of sepsis using the sequential organ failure assessment score. Patients with sepsis may present with an abnormal body temperature, respiratory distress, circulatory changes, abnormal consciousness, and other symptoms. Patients with suspected sepsis should undergo microbiological analysis within the first 45 minutes.[68] It has been reported that 42% of sepsis cases are culture negative, suggesting that many cases are caused by nonbacterial infections.[69] In the search for evidence of sepsis etiology, relevant tests, such as antigenic testing, molecular testing, serological tests, histopathology, and immunohistochemistry, should be completed. Many biomarkers have been used to diagnose sepsis and predict

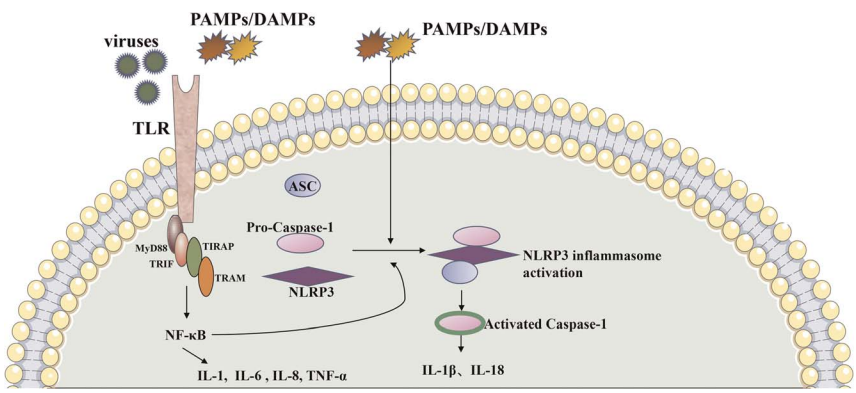

Figure 1. Pathophysiological features of cytokine storm. TLR and NLRP3 can recognize PAMP and DAMP to induce the production of inflammatory cytokines. ASC, apoptosis-associated speck-like protein; DAMP, damage-associated molecular patterns; IL-1, interleukin-1; IL-6, interleukin 6; IL-8, interleukin-8; MyD88, myeloid differentiation protein 88; NLRP3, NOD-like receptor family pyrin domain-containing protein 3; PAMP, pathogen-associated molecular patterns; TIRAP, toll/interleukin-1 receptor (TIR) domain-containing adapter protein; TLR, toll-like receptors; TNF-α, tumor necrosis factor α; TRAM, TRIF-related adaptor molecule; TRIF, toll/interleukin 1 receptor domain-containing adapter-inducing interferon β.

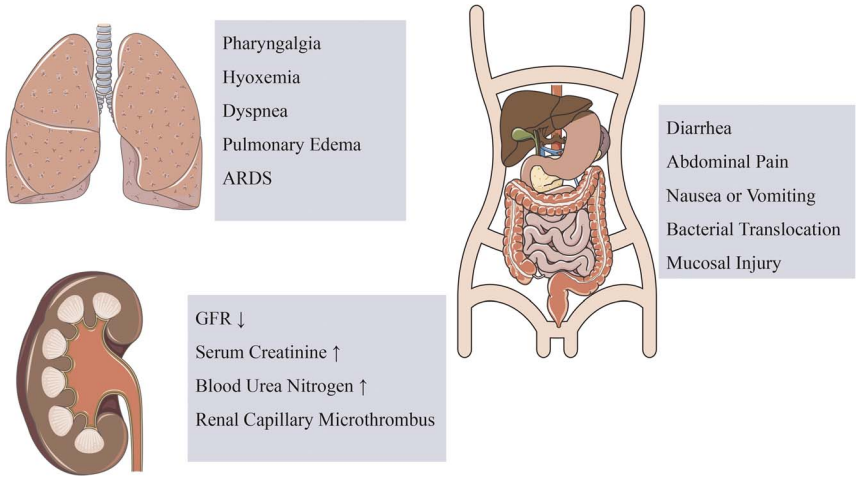

Figure 2. Clinical manifestations of major organ systems in viral sepsis. ARDS, acute respiratory distress syndrome; GFR, glomerular filtration rate.

outcomes. Common biomarkers include procalcitonin, C-reactive protein, lactate, cytokines, and immunoglobulins.[68,70,71] In recent years, next-generation sequencing has been used to identify potential bacterial and viral infections in sepsis.[72] A retrospective study based on metagenomic next-generation sequencing illustrated that concurrent viral load was closely related to the survival rate of patients with sepsis.[73] Table 2 summarizes the common diagnostic methods used for viral sepsis. When a patient with sepsis has no evidence of bacterial, parasitic, or fungal infection, viral sepsis should be considered, and the virus type should be determined as soon as possible.

Treatment of viral sepsis

Supportive treatment

Many deaths in patients with sepsis occur in the first 48–72 hours of treatment; therefore, early identification, reasonable resuscitation, and treatment are crucial for improving the condition of patients with sepsis.[84–86] Supportive treatments for sepsis include monitoring vital signs, fluid resuscitation, lung-protective ventilation, nutrient supply, glucose management, and maintaining the balance between electrolytes and acid base.[87] Early fluid resuscitation is necessary to maintain the balance of water, electrolytes, acids, and bases. However, excess fluid can cause a net positive fluid balance that increases intracardiac pressure, organ edema, and arterial vasodilation.[88] The use of an oxygen mask or tracheal intubation in the early stages can reduce oxygen consumption and protect the airway.[89] Metabolic abnormalities are commonly observed in patients with sepsis. The current consensus for the management of serum glucose is to maintain a serum glucose level of 180 mg/dL.[90] The nutritional treatment of hypermetabolic patients with sepsis remains challenging. Many studies have indicated that, although purposeful underfeeding during sepsis may seem counterintuitive, it

Table 2

Common Diagnostic Methods for Viral Sepsis

Diagnostics	Value of Diagnosis	Disadvantage
Polymerase chain reaction	Rapid, simple, inexpensive	Due to its target specificity, unselected viruses may be missed; requiring auxiliary testing and virus identification by trained personnel[74]
Next-generation sequencing	High sensitivity, fast turnaround time. Drug resistance gene information can be identified; can detect several different targets simultaneously; discovery of new or unexpected viral infection; ability to detect any portion of the genome; the detection rate is significantly higher for bacterial, mixed, viral, and pneumocystis infections[75,76]	Expensive, time consuming, not all genomes are available, prone to contamination with environmental species
Biomarkers		
Lactate	Screen clinically suspected patients,[77] guide resuscitation to reduce mortality[78]	Low sensitivity and specificity[78]
Procalcitonin	Not increased in viral infection[68] Early diagnosis, inexpensive, and easy to obtain	Limited specificity[79]
C-reactive protein	Detect the presence of inflammatory or infectious agents[80]	Reaching the peak levels slowly and last for several days, limited specificity, having no correlation with the severity of sepsis[71]
Cytokines	Have correlation with the severity of the process; IL-6 has better diagnostic and prognostic value than those of PTX3 and PCT[81]	Nonspecific
Pancreatic stone protein	The only biomarker with the ability to discriminate between clinical severity and predict mortality (compared with CRP, PCT, IL-6, and WBC).[82,83]	

CRP, C-reaction protein; IL-6, interleukin 6; PTX3, pentraxin 3; WBC, white blood cell.

Table 3

Treatment of COVID-19 Viral Sepsis

Drugs	Indications	Dosage	Adverse Effects	References
Corticosteroids (strong recommendation)				
Dexamethasone	Severe and critically ill cases	6-mg intravenous injection for 10 d or equivalent	Hyperglycemia, secondary infection, psychiatric disorders, avascular necrosis	[90]
Antivirals				
Remdesivir (weak recommendation)	For adults with severe COVID-19 who do not require mechanical ventilation	Intravenous injection, 200 mg on day 1 followed by 100 mg daily for up to 9 d	Elevation of liver enzymes, increased oxygen requirement, hyperglycemia	[107,108]
Immunotherapy				
Tocilizumab	Severe COVID-19	400- to 800-mg intravenous injection	Infections, nausea, abdominal pain, mouth ulceration and gastritis	[109,110]
Baricitinib	Patients with COVID-19	4-mg daily dose for 14 days	Infections, thrombotic events	[90,111]
Anticoagulant therapy (strong recommendation)				
Enoxaparin	For adults with severe or critical COVID-19	40-mg subcutaneous injection once a day	Ecchymosis and skin necrosis due to vasculitis, urticaria, angioedema and erythema	[112,113]
Apixaban	For adults with severe or critical COVID-19	2.5 mg, oral twice daily	The increased risk of bleeding, thrombocytopenia and nausea, vasculitis and skin necrosis	[113,114]

COVID-19, coronavirus disease 2019.

may benefit patients with hypermetabolism by preventing hyperglycemia and hyperlipidemia.[91] A previous study reported that vitamin C reduced mortality in patients with sepsis. Daily vitamin C supplementation is recommended for patients at high risk of viral infection and sepsis.[92] Early supportive care in sepsis patients is beneficial for preserving vital organ function and reducing mortality.

Antivirus treatment

Antiviral therapy is a top priority in sepsis management, and antiviral drugs should be administered as early as possible in patients with viral sepsis. Antiviral therapy should be initiated to suppress viral replication and reduce the viral load in the early stages of viral sepsis. Broad-spectrum antiviral drugs such as ribavirin and arbidol can target viral entry and replication or modulate cellular defense systems.[93] Ribavirin is recommended for patients with rhinovirus and RSV infections as well as for those with rhinovirus, RSV, adenovirus, and parainfluenza virus infections.[94] Prophylactic use of acyclovir can reduce mortality in patients with herpes simplex virus type 1.[95] Pleconaril is an antiviral drug that fights enteroviruses and rhinoviruses by binding to viral capsids to prevent their adsorption and cell penetration. In a clinical trial of neonatal enterovirus sepsis, the pleconaril group showed lower overall mortality than the placebo.[96] Although the diagnosis of viral sepsis is helpful in reducing the use of unnecessary antibiotics, it should also be noted that severe viral infections can be complicated by or secondary to bacterial infections in clinical practice. Antibiotics should also be selected according to the situation of patients with sepsis.

Immunotherapy

In recent years, immunomodulatory therapy, which aims to promote the clearance of pathogens, thereby preventing severe infections caused by rapid pathogen proliferation, has become increasingly popular for the treatment of sepsis. There have been many studies on immunoregulatory therapy for sepsis; however, there is little consensus regarding the use of immunomodulatory drugs. Immunotherapy should be targeted at suppressing exaggerated inflammation while retaining moderate inflammatory.[97] Corticosteroids, which are traditional anti-inflammatory drugs, are a double-edged sword in the treatment of sepsis. Corticosteroids are recommended only when septic shock cannot be corrected with adequate fluid resuscitation and vasopressors.[98] Antibodies against IL-6 have become effective drugs for the treatment of COVID-19. Tocilizumab, an IL-6 receptor antagonist, reduces the risk of progression to severe ARDS.[99] Many studies have reported that recombinant IL-7 can reverse the basic immune deficiency in sepsis and significantly improve the survival rate.[100–102] PD-1 and PD-L1 are broadly expressed in immune, endothelial, and bronchial epithet.[103] A continuous increase in PD-1 levels in patients with sepsis is closely associated with mortality.[104] PD-1 is involved in the development of the immunosuppressive phase of sepsis by inducing apoptosis of effector T lymphocytes, and its ligand is an ideal target for the treatment of viral sepsis.[105,106] Table 3 summarizes the treatments for COVID-19–related viral sepsis. The principle of immunotherapy is to reduce damage to immune function and avoid rebound inflammation.

Conclusion

Viral sepsis is difficult to diagnose. There is little difference in the clinical manifestations of the different causes of sepsis. Because of its complex manifestations, viral sepsis can cause serious damage to multiple organs. Modern etiological identification methods that effectively distinguish viral from bacterial sepsis will facilitate the development of a new generation of drugs to treat sepsis in the future. In addition, the prognosis of patients with viral sepsis should be a primary concern in future studies.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Zhang Y conceived the topic and scope of the study. Li J and Luo Y wrote the manuscript. Li H and Yin Y critically revised the manuscript. All the authors have read and approved the final version of the manuscript.

Funding

None.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

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How to cite this article: Li J, Luo Y, Li H, Yin Y, Zhang Y. Research progress of viral sepsis: etiology, pathophysiology, diagnosis, and treatment. *Emerg Crit Care Med*. 2023;4(2):74–81. doi: 10.1097/EC9.0000000000000086