Respiratory viral sepsis: epidemiology, pathophysiology, diagnosis and treatment

Xiaoying Gu1,2,3, Fei Zhou1,2, Yeming Wang1,2, Guohui Fan1,2,3 and Bin Cao1,2,4,5

Affiliations: 1Dept of Pulmonary and Critical Care Medicine, National Clinical Research Center of Respiratory Diseases, China-Japan Friendship Hospital, Beijing, China. 2Institute of Respiratory Medicine, Chinese Academy of Medical Science, Beijing, China. 3Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing, China. 4Dept of Respiratory Medicine, Capital Medical University, Beijing, China. 5Tsinghua University-Peking University Joint Center for Life Sciences, Beijing, China.

Correspondence: Bin Cao, Dept of Pulmonary and Critical Care Medicine, National Clinical Research Center of Respiratory Diseases, China-Japan Friendship Hospital, 2 East Yinghua Street, Beijing, 100029, China. E-mail: caobin_ben@163.com

The disease burden of sepsis from viruses is great. Although current understanding of sepsis has improved, the differences between viral and bacterial sepsis were not well understood. It is urgent to pay more attention to respiratory viral sepsis.

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ABSTRACT According to the Third International Consensus Definition for Sepsis and Septic Shock, sepsis is a life-threatening organ dysfunction resulting from dysregulated host responses to infection. Epidemiological data about sepsis from the 2017 Global Burden of Diseases, Injuries and Risk Factor Study showed that the global burden of sepsis was greater than previously estimated. Bacteria have been shown to be the predominant pathogen of sepsis among patients with pathogens detected, while sepsis caused by viruses is underdiagnosed worldwide. The coronavirus disease that emerged in 2019 in China and now in many other countries has brought viral sepsis back into the vision of physicians and researchers worldwide. Although the current understanding of the pathophysiology of sepsis has improved, the differences between viral and bacterial sepsis at the level of pathophysiology are not well understood. Diagnosis methods that can broadly differentiate between bacterial and viral sepsis at the initial stage after the development of sepsis are limited. New treatments that can be applied at clinics for sepsis are scarce and this situation is not consistent with the growing understanding of pathophysiology. This review aims to give a brief summary of current knowledge of the epidemiology, pathophysiology, diagnosis and treatment of viral sepsis.

Introduction

Sepsis is a complex syndrome that results from infection. Recognising sepsis as not just an inflammatory disorder was one of the key reasons to revise previous criteria of sepsis, which had the limitation of low specificity of systemic inflammatory response syndrome as one of the criteria for sepsis [1–3]. According to the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) in 2016, sepsis was defined as a life-threatening organ dysfunction resulting from dysregulated host responses to infection, with the Sequential Organ Failure Assessment (SOFA) score evaluating the degree of organ dysfunction [4, 5]. The definition of sepsis in Sepsis-3 is similar to the previous definition of severe sepsis in Sepsis-2. A meta-analysis incorporating 27 studies from seven high-income countries showed that the incidence rate and case fatality ratio of severe sepsis were 270 per 100 000 person-years and 26%, respectively (Sepsis-2 definition) [6]. The latest data from the 2017 Global Burden of Diseases, Injuries and Risk Factor Study
showed that 48.9 million incident cases of sepsis and 11.0 million sepsis-related deaths were reported globally in 2017, with the highest age-standardised incidence and mortality of sepsis occurring in areas with the lowest socio-demographic index [7]. The global burden of sepsis is larger than previously estimated and may continue to be great because of a prolonged life expectancy and an ageing population [8–11]. In 2017, the World Health Organization and World Health Assembly recognised sepsis as a global health priority, and adopted a resolution to improve the prevention, diagnosis and management of sepsis [12].

Bacteria have been shown to be the predominant pathogens of sepsis caused by infection [9]. The reported proportions of gram-positive and gram-negative organisms among adult septic patients were both around 40%, while the reported proportions of viruses were very low [13, 14]. However, the proportion of negative cultures was up to 42% among patient with sepsis, for whom the possible cause could be virus [15]. Recent studies showed that respiratory viral infections were underdiagnosed in patients with sepsis or septic shock [16, 17]. In both these studies, conducted in three middle-income countries from Southeast Asia and in a rural area of a high-income country (Sweden), viruses were detected in around one-third of adult patients with sepsis. The viruses, which can cause severe disease, included influenza A and B, respiratory syncytial virus, coronavirus, human metapneumovirus, parainfluenza virus types 1–3, adenovirus, enteroviruses, and rhinovirus [18–20]. Our CAP-China study, which was conducted in 34 hospitals from 10 provinces of mainland China, showed that the proportions of patients with community-acquired pneumonia (CAP) who developed sepsis during hospitals were 40.1 and 39.6% among those with influenza and non-influenza viral infections, respectively [18]. As well as for commonly detected viruses, emerging novel virus infections can also result in sepsis and have raised global health concerns [20], these include: severe acute respiratory syndrome-coronavirus (SARS-CoV) [21]; Middle East Respiratory Syndrome-coronavirus (MERS-CoV) [22]; and SARS-CoV-2 which caused the recent outbreak of the coronavirus disease 2019 (COVID-19) in China and in many other countries all over the world.

According to the Surviving Sepsis Campaign, intravenous antibiotics within 1 h after recognition of both sepsis and septic shock is strongly recommended [23]. This recommendation was based on previous findings that a delay in first antibiotic administration was associated with an increased in-hospital mortality [24, 25]. Apart from the benefit of empirical antibiotic use for patients with sepsis, a more precise prescription of antimicrobial therapy, including antiviral therapy for patients without bacterial infection, should be further explored [26]. It is urgent to pay more attention to the role a virus plays in sepsis. The most common sites of infection among patients with sepsis are the respiratory tract (64%) [27]. Nevertheless, the proportion of negative cultures for the bacteria was 9.8%, while the reported proportions of viruses were very low [13, 14]. Bacteria have been shown to be the predominant pathogens of sepsis caused by infection [9]. The reported proportions of gram-positive and gram-negative organisms among adult septic patients were both around 40%, while the reported proportions of viruses were very low [13, 14]. However, the proportion of negative cultures was up to 42% among patient with sepsis, for whom the possible cause could be virus [15]. Recent studies showed that respiratory viral infections were underdiagnosed in patients with sepsis or septic shock [16, 17]. In both these studies, conducted in three middle-income countries from Southeast Asia and in a rural area of a high-income country (Sweden), viruses were detected in around one-third of adult patients with sepsis. The viruses, which can cause severe disease, included influenza A and B, respiratory syncytial virus, coronavirus, human metapneumovirus, parainfluenza virus types 1–3, adenovirus, enteroviruses, and rhinovirus [18–20]. Our CAP-China study, which was conducted in 34 hospitals from 10 provinces of mainland China, showed that the proportions of patients with community-acquired pneumonia (CAP) who developed sepsis during hospitals were 40.1 and 39.6% among those with influenza and non-influenza viral infections, respectively [18]. As well as for commonly detected viruses, emerging novel virus infections can also result in sepsis and have raised global health concerns [20], these include: severe acute respiratory syndrome-coronavirus (SARS-CoV) [21]; Middle East Respiratory Syndrome-coronavirus (MERS-CoV) [22]; and SARS-CoV-2 which caused the recent outbreak of the coronavirus disease 2019 (COVID-19) in China and in many other countries all over the world.

Epidemiology of respiratory viral sepsis

Pneumonia was found to be the most common cause of sepsis and septic shock [14, 29]. A recent retrospective cohort study that included hospitalised patients diagnosed as viral CAP without bacterial co-infection showed viral sepsis was present in 61% of these patients [30]. According to previously published data, 100 million cases of viral CAP occur every year in adults globally [31], so we can speculate the disease burden of viral sepsis is huge. The most common virus detected among patient with viral sepsis was influenza A virus, followed by rhinovirus, parainfluenza virus types 1–3, respiratory syncytial virus, adenovirus, influenza B virus and coronavirus [30]. A positive pathogen result for a virus is not sufficient for the diagnosis of viral sepsis. Whether the virus detected caused sepsis or not, such as being a coinfection of an unknown pathogen, leading to secondary infection of the other pathogen, or being just a false-positive result, needs to be decided by physicians according to clinical features and both laboratory and radiographic results of the patient [28, 32, 33].

Influenza virus related sepsis

Influenza viruses, including influenza A and B, can cause both seasonal epidemics and out-of-season sporadic cases and outbreaks [34]. The annual attack rate of influenza was estimated to be around 10% among adults [34, 35]. Most people have self-limited upper respiratory tract symptoms, while some people develop severe illness. Seasonal influenza epidemics were estimated to account for about 291243–645832 respiratory deaths annually, with the highest mortality rate in sub-Saharan Africa and southeast Asia [36]. A retrospective cohort study using hospitalisation data and influenza surveillance data from the USA found that the incidence rate of influenza-associated severe-sepsis hospitalisation was 8.8 per 100000 person-years (95% CI 3.9–16.5) [37]. Severe sepsis was present in 73% of influenza-associated critical illness hospitalisations defined as any hospitalisations with acute respiratory failure, severe sepsis, or in-hospital death.

A recent study showed that the most commonly detected virus among viral CAP patients who developed viral sepsis without bacterial co-infection was the influenza A virus, with a detection rate around seven
times that of influenza B (52% versus 7%) [30]. This may be due to different virulences of different strains of influenza virus and the specific host response to them [38, 39]. Previous studies also provide epidemiological data for sepsis related to different subtypes of influenza A virus [40–43]. Data from 26 patients infected with influenza A (H7N9) virus from one province in China showed that 10 (38.5%) developed septic shock quickly after the onset of illness, which was independently associated with mortality after multivariable adjustment [40]. For hospitalised patients infected with the 2009 pandemic influenza A(H1N1) (H1N1pdm09), the relative risk of sepsis and septic shock was 1.70 (95% CI 1.46–1.97) compared with hospitalised patients infected with seasonal influenza [41]. Furthermore, one study conducted among hospitalised patients with H1N1pdm09 showed that the proportion of sepsis was higher among patients with pneumonia than those without (18% versus 3%) [42]. The study results listed above not only provide epidemiological characteristics of influenza but also highlight that patients diagnosed with pneumonia during the pandemic season of influenza should be paid more attention by physicians because they are more likely to develop sepsis.

Coronavirus-related sepsis
The emerging novel coronavirus outbreak in China and many other countries worldwide has brought coronavirus back into our vision. To date, seven types of coronavirus are known to cause human disease, with four of them causing mild infections, while the other three betacoronaviruses, including SARS-CoV, MERS-CoV, and the recently isolated SARS-CoV-2, cause fatal cases [20, 44, 45]. SARS-CoV and MERS-CoV have caused 10,590 cases together, with 1632 being fatal cases. As of 10 June 2020, 84,652 cases of SARS-CoV-2 infection were confirmed in China, of which 4645 were fatal [46]. Another 1797 imported cases from overseas were reported. In other countries, territories or areas outside China, as of 10 June 2020, more than seven million COVID-19 cases were also confirmed, of which 403,380 were fatal [47].

Drosten et al. [22] reported that a 73-year-old man infected with MERS-CoV developed renal insufficiency and required dialysis on day 14 after onset of symptoms. With haemolysis and acute coagulation disorder, this patient died on day 18 due to septic shock. Infections with SARS-CoV were also reported to result in sepsis [21]. According to data from the first 41 cases infected with SARS-CoV-2, platelet counts were decreased while bilirubin and creatinine were elevated in several patients, which were signs of coagulation disorder, liver and renal dysfunction, respectively [20]. These patients can be diagnosed as having sepsis with the updated Sepsis-3 definition. Our recent study included 191 laboratory-confirmed COVID-19 patients in Wuhan who were discharged or died as of 31 January 2020. No bacterial pathogen was detected among these patients on admission. The results showed that the proportions of patients with sepsis and septic shock were 59% and 20%, respectively. All patients who died and 42% of patients who were discharged developed viral sepsis during hospitalisation. The median (interquartile) time from illness onset to sepsis was 9.0 (7.0–13.0) days [48].

Other respiratory virus-related sepsis
Among susceptible populations with sepsis, almost any virus could be detected, including respiratory viruses (e.g. rhinovirus, parainfluenza virus types 1–3, respiratory syncytial virus, adenovirus, coronavirus and cytomegalovirus) and other viruses (e.g. dengue viruses, hantaviruses, rotavirus and bocavirus) [17, 22, 30, 48–55]. We mainly focus on respiratory viruses related to sepsis. Our study results from CAP-China found the risk of sepsis during hospitalisation between CAP patients with influenza and those with non-influenza respiratory virus infection were not statistically different (OR 1.00 (95% CI) 0.63–1.58) [18]. Previous studies showed diverse positive rates of non-influenza virus for patients with different clinical characteristics. Among viral CAP patients without bacterial co-infection and severe immunosuppression who developed viral sepsis, the most frequently detected non-influenza respiratory virus was rhinovirus (14%), followed by parainfluenza virus types 1–3 (11%), respiratory syncytial virus (10%), adenovirus (8%), and coronavirus (1%) [30]. Cytomegalovirus is one of the most common viral pathogens detected in immunocompromised patients. In the study conducted among Ugandan adults with sepsis of whom 84% were infected with HIV, the most common respiratory virus detected was cytomegalovirus, with a positive rate of 41% [56]. After multivariable adjustment, cytomegalovirus was associated with in-hospital mortality (OR 3.2; 95% CI, 2.1–10.0). A previous meta-analysis that included studies conducted among immunocompetent patients also suggested that cytomegalovirus was more likely to be detected among patients with severe sepsis or septic shock than mixed patients with or without severe sepsis (32% versus 15%) [57]. These results indicate that the specific pathogen spectrum among different populations may be attributable to, but not limited to, the clinical characteristics of study populations, such as immune status.

The aetiological and causal relevance of both influenza and non-influenza respiratory viruses with sepsis is still challenging and needs to be further identified among other prospective cohort studies. Studies conducted in both immunocompetent and immunocompromised hosts that can characterise host responses to viral infections are also needed to better determine causality.
Pathophysiology of respiratory viral sepsis

Respiratory viral sepsis is a highly heterogeneous and multifaceted syndrome characterised by an overwhelming and systemic dysregulated host immune response to respiratory viral infection, with organ dysfunction including, but not limited to, the lung. Previous studies provided evidence for extrapulmonary organ dysfunction caused by respiratory viral infection: e.g. acute kidney injury and cardiac injury among cases with influenza infection; acute kidney injury and thrombocytopenia reported for MERS-CoV infection; high viral loads in the gut and liver and moderate viral loads in the kidney among fatal cases with SARS-CoV infection; and liver dysfunction reported for respiratory syncytial virus infection [58–62]. The recent findings from our study showed that around half of the COVID-19 fatalities developed acute kidney injury, heart failure or coagulopathy [48]. In another recent study that included 183 COVID-19 patients, disseminated intravascular coagulation was observed in 71.4% of fatal cases, and in 0.6% of non-fatal cases [63]. The multi-organ dysfunction determines that viral sepsis is a more complicated clinical status than severe viral pneumonia, with inflammation in the lung which is the primary and specific target organ of the respiratory virus. The type of infection and host response to the specific pathogen are determinants of sepsis and closely related to prognosis after the development of sepsis. The pathophysiology of sepsis includes that the immune response initiated by an invading pathogen fails to return to homeostasis, and thus culminating in a pathological syndrome that is characterised by sustained excessive inflammation and immune suppression [64].

The initial sensing of the host innate system after infection is to recognise pathogen-associated molecular patterns mediated by innate pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), retinoic acid-inducible gene-1 like receptors, NOD-like receptors, and C-type lectin receptors [65, 66]. For most of the infections, the host innate immune system can eliminate the pathogen through pro-inflammatory responses, including the release of cytokines and chemokines (tumour necrosis factor (TNF), interleukin (IL)-1β, IL-12 and IL-18), the recruitment of phagocytes, and the local activation of the complement and coagulation systems [64, 66, 67]. Among patients with sepsis, pathogens cannot be eliminated by the host immune system and the homeostasis of the host immune system is disturbed, resulting in both an excessive inflammation and immune suppression.

The excessive inflammation of sepsis is mediated through the release of pro-inflammatory mediators by leukocytes and parenchymal cells [68–71]. Leukocyte and parenchymal cell injury results in the release of damage-associated molecular patterns, further disrupting the host response by activating many of the PRRs [72, 73]. These PRRs can also recognise pathogen-associated molecular patterns, leading to a vicious cycle that also involves organ damage and dysfunction. The coagulation system, complement system, neutrophils and vascular endothelium are also activated in this stage [74–77]. In the immune suppression stage, both adaptive and innate immune systems are involved. This stage is characterised by the apoptosis of T-cells, B-cells and dendritic cells, the exhaustion of T-cells, and the expansion of regulatory T-cell and myeloid-derived suppressor cell populations [78–80]. Patients with sepsis have increased numbers of myeloid-derived suppressor cells, which are immature myeloid cells that can impede immune responses, particularly T-cell function. Reprogramming of antigen-presenting cells leads to a reduced HLA-DR expression and a diminished capacity to produce pro-inflammatory cytokines [81]. The most important findings in sepsis are the delayed apoptosis of neutrophils and the appearance of immature band-like neutrophils in peripheral blood that have deficits in antimicrobial effector functions [64].

Host immune response to respiratory virus

The causes and characteristics of sepsis can be highly heterogeneous [64]. However, few studies provide evidence as to whether the pathophysiology of viral sepsis is different from that of bacterial sepsis, mainly because of the limited studies conducted that focus on viral sepsis. Current knowledge of the pathophysiology of respiratory viral sepsis is limited to the specific immune responses to viral infection.

For the influenza virus, haemagglutinins of different strains determine attachment to the epithelium of which specific part of the airway, and the viral polymerase complex is associated with different levels of viral replication and cytokine production in the infected epithelial cells [39, 82, 83]. Seasonal influenza, such as H3N2 and H1N1, targets preferential epithelium in the large airways (trachea, bronchi and bronchioles) by binding to α2,6-sialylated glycans, while H1N1pdm09 and H5N1 tend to infect both large airways and alveoli by binding to α2,3-sialylated glycans of pneumocytes [84–88]. Furthermore, mutation in the haemagglutinins of influenza leads to alteration of the cell tropism. The mutation of haemagglutinins of H5N1 results in the ability to bind not only α2,3- but also α2,6-sialylated glycans of pneumocytes [39, 88, 89]. Mutation in the viral RNA polymerase complex could result in better viral replication or increased secretion of pro-inflammatory cytokines [39].

Viral infections, such as the influenza virus, can also trigger initial sensing of the host innate system and recruitment of leukocytes through PRRs [90]. These PRRs include TLR-3, TLR-4, TLR-7, and RIG-I, the
The interaction of influenza with increased mortality [38, 64]. Previous studies showed the interaction between viral and bacterial infection. Immune suppression can also increase the probability for secondary bacterial infections, which is associated with reactivation, which refers to the process of a latent virus switching to a lytic phase of replication. Immune adaptive immunity following excessive inflammation in almost all forms of sepsis gives way to viral interaction of bacterial and viral infection for sepsis immune suppression in patients with sepsis needs to be further demonstrated. [103]. Whether cytomegalovirus reactivation plays a role for disease progression or is only a marker of association between cytomegalovirus reactivation and host response biomarkers, including IL-6, IL-10, interferon-gamma-induced protein-10 or IL-1 receptor antagonist, was found among patients with sepsis [102]. However, definite evidence and a mechanism for this relationship are still not clear, cytomegalovirus reactivation and clinical outcomes among immunocompetent patients with sepsis [101]. Previous studies provided the possibility for the causal relationship between cytomegalovirus reactivation and clinical outcomes among immunocompetent patients with sepsis [28, 100]. The potential mechanisms with cellular microRNAs produced by the human genome, sharing the regulation of the same signalling pathways and regulating the same spectrum of microRNAs. For cytomegalovirus, the proportion of its reactivation in immunocompetent patients was around 30% and has become an area of increasing interest in recent years [101]. Previous studies provided the possibility for the causal relationship between cytomegalovirus reactivation and clinical outcomes among immunocompetent patients with sepsis [102]. Whether cytomegalovirus reactivation plays a role for disease progression or is only a marker of immune suppression in patients with sepsis needs to be further demonstrated.

Viral reactivation may also play a role in the prognosis of sepsis. Immune exhaustion during sepsis provides the probability for some latent infections to escape immunological control, and replicate under this more forgiving environment [28]. Some reactivated viral infections, such as the Epstein–Barr virus, were reported to be associated with clinical outcomes among patients with sepsis [28, 100]. The potential mechanism is that reactivated viral microRNAs might be involved in sepsis by functional mimicry mechanisms with cellular microRNAs produced by the human genome, sharing the regulation of the same signalling pathways and regulating the same spectrum of microRNAs. For cytomegalovirus, the proportion of its reactivation in immunocompetent patients was around 30% and has become an area of increasing interest in recent years [101]. Previous studies provided the possibility for the causal relationship between cytomegalovirus reactivation and clinical outcomes among immunocompetent patients with sepsis [102]. Whether cytomegalovirus reactivation plays a role for disease progression or is only a marker of immune suppression in patients with sepsis needs to be further demonstrated.

Interaction of bacterial and viral infection for sepsis
As mentioned previously, immune suppression characterised by a decreased function in both innate and adaptive immunity following excessive inflammation in almost all forms of sepsis gives way to viral reactivation, which refers to the process of a latent virus switching to a lytic phase of replication. Immune suppression can also increase the probability for secondary bacterial infections, which is associated with increased mortality [38, 64]. Previous studies showed the interaction between viral and bacterial infection. The interaction of influenza with Streptococcus pneumoniae and Staphylococcus aureus (including methicillin-resistant S. aureus) was observed and can be reflected by an increased bacterial coinfection during seasonal epidemic and pandemic outbreaks of influenza. A previous study showed that bacterial coinfection was identified in approximately one-third of fatal pandemic H1N1 cases, with S. pneumoniae identified in 45.5% of cases and S. aureus in 31.8% of cases (including 71.4% of the S. aureus as methicillin-resistant S. aureus) with bacterial coinfection [104]. Not only for influenza, respiratory syncytial virus was also reported to increases the virulence of S. pneumoniae [105]. Several mechanisms can provide clues to the predisposition of bacterial infection after respiratory viral infections. Respiratory viruses can damage the respiratory epithelium and the basement membrane of the epithelium is exposed, to which bacteria can adhere [106]. Platelet-activating factor receptor upregulated by released pro-inflammatory cytokines can provide a receptor for pneumococcal adherence and invasion [106, 107]. In addition, antibacterial defence mechanisms can be impaired by influenza through increasing neutrophil apoptosis, and neutrophil and monocyte dysfunction [108, 109]. This epidemiological evidence and the possible mechanisms provide indirect or direct evidence for bacterial reactivation at the stage of immune suppression among patients with viral sepsis.
Diagnosis of respiratory viral sepsis

The diagnosis of respiratory viral sepsis depends on two steps: one step is the diagnosis of sepsis using the SOFA score, and the other important and challenging step is identifying the cause of the sepsis as a respiratory virus. The differentiation between bacterial and viral sepsis, especially at the initial stage after the development of sepsis, is important for the treatment of sepsis and prevention of mortality from sepsis. However, no golden standard was identified to broadly and efficiently determine and differentiate the presence and type of infection.

Pathogen detection is the most important step of differential diagnosis between respiratory viral and bacterial sepsis. Point-of-care testing and next-generation sequencing provide the possibility for a quick and accurate identification of the potential pathogen that is causing the sepsis. Next-generation sequencing is especially important for confirmation of infection by novel viruses. The role next-generation sequencing played in the laboratory confirmation of SARS-CoV-2 infection is important. Testing multiple pathogens in one test and saving time are the advantages of point-of-care testing, which are especially important for sepsis [110]. Furthermore, the use of point-of-care testing for sepsis was not limited to pathogen detection, but was also used for blood plasma protein quantification (e.g. C-reactive protein and procalcitonin) and leukocyte monitoring (through antibody capture or intrinsic property characterisation) [111]. Clinical characteristics, blood biomarkers including C-reactive protein and procalcitonin, were not fully demonstrated to clearly discern viral and bacterial infection among patients with pneumonia, while the discrimination ability among patients with sepsis needs to be further demonstrated [112].

To distinguish infection compared to inflammation in the absence of infection and viral infection as compared to bacterial infection, several transcriptomics studies have been conducted to determine the presence of infection as compared to inflammation without infection [113], as well as to distinguish between the presence of bacterial and/or viral infection [114–117]. Some of these studies derived and validated models focusing on gene sets that can distinguish between viral and bacterial infection [117, 118]. However, the many genes required for these models enlarged the difficulty to translate them into practical clinical tools. Sweeney and co-workers [113, 114] derived and validated the “Sepsis MetaScore” based on 11 differentially expressed genes and the “Bacterial/viral MetaScore” based on seven differentially expressed genes which can profile the host gene response to build an integrated antibiotics decision model for sepsis. The sensitivities of this model for detecting bacterial infection and the specificity for viral infection were high (94.0% and 90.6%, respectively), but the specificity of this model for detecting bacterial infection and sensitivity for viral infection were not satisfying (59.8% and 53.0%, respectively). These results show the possibility to quickly discriminate between viral and bacterial sepsis and inform future research to identify biomarkers that can be translated to the clinical setting. Stratifying sepsis patients into more homogeneous subgroups should be the key points for future biomarker research, which can be realised with more consideration for pathophysiology of biomarkers.

Treatment of respiratory viral sepsis

Timely intervention is the key to effective treatment among patients with sepsis. These include an initial fluid resuscitation and antibiotic therapy within the first hour [119–121]. In patients with haemodynamic instability after the initial fluid resuscitation, further haemodynamic stabilisation and assessment of fluid responsiveness should be continued [119, 122, 123]. During the disease progression of COVID-19, some patients with viral sepsis have clinical features including cold extremities, weak peripheral pulses and severe metabolic acidosis, while the blood pressure levels remain normal. These clinical features indicate the continuing internal environmental disorders and microcirculation dysfunction among these patients. Thus, haemodynamic stabilisation is necessary and important throughout the progress of treatment for patients with viral sepsis. The recommendation of antibiotic therapy is for all patients with sepsis. As mentioned above, a previous study showed that the proportion of sepsis cases with a negative culture was around 42% [15]. Future studies to evaluate effectiveness of antibiotic use and potential antibiotic resistance among these patients are needed, as inappropriate prescription can increase antibiotic resistance.

Pathogen-directed therapy should be the emphasis during treatment for patients with sepsis. For patients with suspected or confirmed respiratory viral sepsis, the early initiation of antiviral drugs with inhibiting viral replication and decreasing viral load is the most important step. Around 90 antiviral drugs have been formally approved for the treatment of human infectious diseases over the past 50 years, covering viruses that could cause viral sepsis, such as the influenza virus, human cytomegalovirus and respiratory syncytial virus [124]. However, studies with these antiviral drugs were rarely conducted to evaluate the effectiveness for respiratory viral sepsis, which should be the focus of future research. Current findings indicate the potential effect of baloxavir, oseltamivir, peramivir and zanamivir for influenza infections and cidofovir for adenovirus infections in immunocompromised patients [125]. Furthermore, the broad-spectrum antiviral
drug ribavirin for the treatment of immunosuppressed patients with rhinovirus and respiratory syncytial virus infections, and arbidol for rhinovirus, respiratory syncytial virus, adenovirus and parainfluenza virus infections were also suggested. The broad-spectrum antiviral drugs, which refer to antivirals targeting viral entry and replication or modulating cellular defence systems, should be distinguished from broad-spectrum antibiotics which act against both gram-positive and gram-negative bacteria. To our knowledge, the potential effectiveness of ribavirin for rhinovirus infection and cidofovir for adenovirus infection were only indicated by several case reports, and need to be further demonstrated. Faced with the great challenge brought by SARS-CoV-2, our research group initiated two randomised controlled trials to evaluate the effectiveness and safety of remdesivir among COVID-19 patients, with one conducted among severe patients (clinicaltrials.gov identifier NCT04257656) and the other one among mild and moderate patients (clinicaltrials.gov identifier NCT04252664) [126, 127]. Another trial evaluating the combined use of lopinavir/ritonavir in patients with SARS-CoV-2 infection has been completed (ChiCTR identifier ChiCTR2000029308). Looking back at the history of this infectious disease outbreak, antiviral treatment is the most important and powerful weapon to fight against the emerging and re-emerging viral pathogen, which should be a continuous focus of future research.

The potentially beneficial effects from the early initiation of antiviral treatment and optimal duration of antiviral drugs use among septic patients are not clear, with current study findings limited to severe or critical patients with virus infection. Findings from ICU patients with the H1N1pdm09 virus infection showed the initiation of antiviral treatment within 6 h of admission was associated with shorter lengths of hospital stay [128]. This indicates that antiviral treatment for critically ill patients with suspected pandemic influenza virus infection should be initiated as early as possible without waiting for the pathogen results. The duration of antiviral drug use is also not yet ascertained for the prolonged viral shedding among patients with critical illness [129]. Previous studies recommended the usage of antiviral drugs for at least 5 days and to repeat pathogen testing among patients at high risk of severe and life-threatening disease [130]. Our future understanding of viral sepsis and the effect of the early use of antiviral medicines will provide evidence to guide the use of antiviral drugs among patients with sepsis. As well as the potential role of antiviral drugs for viruses that causes sepsis, they were indicated in some studies to play a role in the treatment of viral reactivation, which can occur in the stage of host immune suppression. Future studies are still needed to evaluate the treatment effects of antiviral drugs for viral reactivation, with potential applications for all types of sepsis [131].

In recent years, an area of great interest to clinicians and the research of sepsis is immunomodulatory therapy for treating the host immune response. Excessive inflammatory responses can be inhibited by immunomodulatory therapy through altering or counteracting host inflammatory mediators, such as TNF and IL-1, or using broad-spectrum anti-inflammatory molecules with non-selective suppression of inflammation [132, 133]. However, previous clinical trials to assess the effect of the inhibition of the excessive inflammatory response of septic patients did not show an improvement in the outcome [134, 135]. Several clinical trials to evaluate the effect of anti-inflammatory agents, such as humanised C5a-specific monoclonal antibody and soluble recombinant human thrombomodulin, are still ongoing and cannot provide available data now [136, 137]. Due to the failure to generate new treatments, immunomodulatory therapy with inhibition of excessive inflammatory response has become less popular, whereas immune stimulants have been advocated to be given to patients with sepsis for the potential effect to reverse immune suppression among sepsis cases [138]. The immune stimulatory system is intended to restore immune functions and promote the rapid clearance of pathogens, and thus reduce the incidence of secondary infections and late sepsis mortality. The use of some immune-stimulating cytokines, such as type II interferon-γ, IL-7, IL-15 and granulocyte-macrophage colony-stimulating factor, has been demonstrated to reverse immunosuppression in animal models or clinical trials [139, 140]. As the immune stimulatory aims to restore immune function and reduce mortality related to secondary infections of sepsis, the application of this treatment should be specific to patients who may benefit from this therapy. The biomarkers, such as the reduced expression of monocyte HLA-DR and increased expression of monocyte programmed death ligand-1, may be considered for selecting patients who can benefit from immune stimulation [79, 141]. Current knowledge of the potential benefit of immune stimulants therapy for sepsis provides clues for the generation of new treatments in the future. However, due to the limited studies of sepsis treatment and the limited attention from researchers and physicians about viral sepsis, there is a long way to go to evaluate the potential use of these relatively novel therapies from bench to bedside. The subtypes of sepsis also need to be fully considered in the studies conducted in the future.

For other therapies, which include glycaemic control and nutritional support for the treatment of sepsis, controversies also exist. The current consensus for the control of glycaemia is to maintain the glycaemic level at <180 mg·dL⁻¹ [23], but to avoid tight glycaemic control because of the potential harm from
hypoglycaemic episodes [142]. Although optimal nutritional support is important in critically ill patients, the timing, dose, duration and route of nutritional support are not clear. Previous studies did not find a superiority of the enteral compared with the parenteral route for association with mortality, but found a greater risk of digestive complications among those who received enteral nutrition [143, 144]. Animal studies showed that anorexia was protective but nutritional supplementation was detrimental in bacterial sepsis, with glucose necessary and sufficient for these effects [145]. In contrast, nutritional supplementation protected against mortality from influenza infection and viral sepsis, while blocking glucose utilisation was lethal. Whether these results can be translated to a clinical setting needs to be further validated among patients with viral or bacterial sepsis.

Conclusions

Sepsis is a heterogeneous syndrome identified as a life-threatening organ dysfunction that results from dysregulated host responses to infection. As pathogens of sepsis, viruses have not been received enough attention by physicians and researchers, which should be altered given the huge burden. Although our current understanding of the pathophysiology of sepsis has improved, the development of new treatments for sepsis seems not to be consistent with the understanding of the pathophysiology. Future studies should not only focus on understanding the host immune response in the development of sepsis, especially viral sepsis, but also explore how to stratify patients into more homogeneous subgroups on the basis of their pathophysiology. The identification of biomarkers that can differentiate who might benefit from a specific intervention can help the application of new treatments into clinics with monitoring the effects of future therapies. The development of antiviral drugs, immunomodulatory and immune stimulants therapy, and vaccine development, given the important role influenza vaccines play, should be the most important perspectives of future research to fight against the epidemic, emerging and re-emerging viral pathogens that can cause respiratory viral sepsis. Furthermore, with the growing knowledge of sepsis and more patients surviving sepsis in the future, the long-term sequelae of sepsis will be another problem for physicians and researchers to consider.

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