

# Influenza Infections and Emergent Viral Infections in Intensive Care Unit

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## Abstract

Critically ill patients are admitted to an intensive care unit (ICU) for multiple reasons. In this study, we aim to analyze the current evidence and findings associated with influenza and other emergent viral infections, namely, herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV), and cytomegalovirus (CMV).

Among medical conditions, community-acquired respiratory infections are the most frequent reason for ventilatory support in ICUs. Community-acquired pneumonia in a severe form including the need of invasive mechanical ventilation and/or vasopressors is associated with high mortality rates. However, after the pandemic that occurred in 2009 by H1N1 influenza, the number of cases being admitted to ICUs with viral infections is on the rise. Patients in whom an etiology would not have been identified in the past are currently being tested with more sensitive viral molecular diagnostic tools, and patients being admitted to ICUs have more preexisting medical conditions that can predispose to viral infections. Viral infections can trigger the dysregulation of the immune system by inducing a massive cytokine response. This cytokine storm can cause endothelial damage and dysfunction, deregulation of coagulation, and, consequently, alteration of microvascular permeability, tissue edema, and shock. In severe influenza, this vascular hyperpermeability can lead to acute lung injury, multiorgan failure, and encephalopathy. In immunocompetent patients, the most common viral infections are respiratory, and influenza should be considered in patients with severe respiratory failure being admitted to ICU. Seasonality and coinfection are two important features when considering influenza as a pathogen in critically ill patients. Herpesviridae (HSV, CMV, and EBV) may reactivate in ICU patients, and their reactivation is associated with morbidity/mortality. However, whether a specific treatment may impact on outcome remains to be determined.

## Keywords

- ▶ community-acquired respiratory infections
- ▶ herpesviridae
- ▶ intensive care unit

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Critically ill patients are admitted to an intensive care unit (ICU) due to multiple reasons. Among medical conditions, community-acquired respiratory infections are the most frequent reason for ventilatory support in ICUs. Community-acquired pneumonia (CAP) in a severe form including the need of invasive mechanical ventilation and/or vasopressors is associated with high mortality rates. The most common etiology is bacterial, with *Streptococcus pneumoniae* causing almost half of the episodes of CAP when the etiology is identified. However, after the pandemic that occurred in 2009 by H1N1 influenza, the number of cases being admitted to ICUs with viral infections is on the rise. Patients in whom an etiology would not have been identified in the past are being tested with more sensitive viral molecular diagnostic tools; in addition, patients currently being admitted to ICU have more preexisting medical conditions that can predispose to viral infections.

In this study, we aimed to analyze the current evidence and findings associated not only with influenza but also with other emergent and often opportunistic viral infections, namely herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV), and cytomegalovirus (CMV).

## Influenza

### Introduction

Influenza viruses belong to the Orthomyxovirus family. They are classified into influenza A, B, and C based on their core proteins. The envelope of the influenza A virus contains two major surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA). HA is responsible for cell attachment and membrane fusion, and NA enables the release of new virions from the cell through its cleaving of the bonds between HA and sialic acid. It also has a role in viral ingress by cleaving sialylated mucins to allow virus penetration through the mucous layer.<sup>1</sup>

Influenza A viruses are subclassified based on the HA and NA glycoproteins. World Health Organization (WHO) nomenclature for the classification of influenza virus consists of the following two parts.<sup>2</sup>

- Type and Strain Designation
- For Influenza A Viruses: A Description of the Antigenic Specificity of the Surface Antigens (H and N)

There are currently 18 subtypes of HA (H 1–18) and 11 subtypes of NA (N 1–11). These mostly circulate in wild birds. There are three combinations that are known to have circulated widely in humans: A/H1N1, A/H2N2, and A/H3N2.<sup>3</sup> The influenza B virus was first isolated in 1940. It circulates solely in humans and has no animal reservoir.<sup>3</sup>

Minor changes in the protein structure of the influenza A virus are known as antigenic drift. These mutations allow the virus to evade the immune system and cause further outbreaks of influenza. Antigenic drifts occur in influenza A, B, and C viruses. The segmented genome of influenza A virus genome allows for the exchange of entire gene segments in the event that two different influenza A viruses simultaneously infect and replicate in the same host cell.<sup>4</sup> Antigenic shift is caused by reassortment of two different subtypes of influenza virus

(such as between an animal and a human subtype), which causes a phenotypic change. Antigenic shift only occurs in influenza A virus as it infects more than just humans. Antigenic shifts can result in epidemics and pandemics. Both the pandemic strains in 1957 and 1968 were derived by genetic reassortment between human and avian viruses.<sup>5</sup>

### Epidemics and Pandemics

Epidemics occur annually and, according to the WHO, result in an estimated 3 to 5 million cases of serious illness and in approximately 290,000 to 650,000 deaths per year. There were three influenza virus pandemics in the 20th century (1918, 1957, and 1968), and one pandemic in the 21st century (2009).<sup>6</sup> The influenza pandemic of 1918 to 1919 was the most catastrophic in recorded history. An estimated one-third of the world's population (~500 million people) were infected with the virus.<sup>7</sup> Total deaths were estimated at around 50 million,<sup>8,9</sup>; however, it is acknowledged that the death toll may have been significantly higher than this and may, in fact, have reached 100 million.<sup>9</sup>

### Origin of Human Pandemic Strains

Influenza viruses in humans originate from birds and swine.<sup>3</sup> The first human influenza A virus was isolated in 1933 and was designated H1N1. This circulated until 1957 when it was replaced by the H2N2 subtype (Asian influenza). In 1968, the Hong Kong (H3N2) virus appeared, after which the H2N2 Asian strains were no longer detectable in humans. Then, in 1977, the H1N1 virus reappeared (likely having escaped from a laboratory).<sup>5</sup> The H1N1 and H3N2 viruses, along with influenza B viruses, have continued to cocirculate in the human population, undergoing considerable evolution through antigenic drift.<sup>3</sup>

### Influenza: Pathophysiology

Influenza virions recognize potential host cells by detecting sialic acid and binding to it using the HA viral glycoprotein.<sup>10</sup> Sialic (N-acetylneuraminic) acid is found on nearly all animal cells. It forms either an  $\alpha$ -2,3 or  $\alpha$ -2,6 linkage, and it is this configuration that is recognized by the HA protein.<sup>10</sup> The  $\alpha$ -2,3 linkage is the major sialic acid found in the gastrointestinal tract of the duck. In contrast, the major sialic acid found in upper respiratory epithelial cells in humans contains the  $\alpha$ -2,6 linkage. It is for this reason that not all avian strains can easily infect humans. For example, in order for avian influenza (H5N1) to infect humans, it must penetrate deep into the alveoli where there are more  $\alpha$ -2,3 receptors.<sup>11</sup> Once the virus attaches to the host cell, it enters the cell through receptor-mediated endocytosis. The envelope fuses with the host cell, and M2 proteins (a target for amantadine) form ion channels, allowing entry of ribonucleoproteins necessary for viral uncoating and replication.<sup>10</sup> Initial response to infection is characterized by proinflammatory state. Th1 cells are activated and release proinflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), and interleukin (IL)-2.<sup>12,13</sup> The secondary phase of infection is characterized by the anti-inflammatory state. It is in this state that activated Th2 cells secrete cytokines such as IL-4 and IL-10.<sup>12,14</sup> It is this state

of depressed immune activation that leads to secondary infections such as bacterial coinfections and CMV reactivation.<sup>15</sup>

The influenza virus has developed its own host of mechanisms to counteract the activity of major antiviral cytokines such as INF- $\gamma$ . Influenza proteins such as NS-1, which antagonize and inhibit the actions of IFN, PBF-F2 proteins that inhibit IFN induction, viral polymerase that inhibits IFN function, and M2 protein prevents TLR induction.<sup>16</sup>

Viral infections can trigger the dysregulation of the immune system by inducing a massive cytokine response. This cytokine storm can cause endothelial damage and dysfunction, deregulation of coagulation, and, consequently, alteration of microvascular permeability, tissue edema, and shock.<sup>17</sup> In severe influenza, this vascular hyperpermeability can lead to acute lung injury, multiorgan failure, and encephalopathy.<sup>16</sup> Different strains of influenza elicit different immune responses. It has been suggested that H5N1 may cause a higher viral load and hypercytokinemia.<sup>18,19</sup> It has also been shown that H5N1 viral replication is not confined to the respiratory tract but also occurs in the intestine.<sup>20</sup>

### Clinical Features

Influenza is an acute respiratory disease characterized in its full form by the sudden onset of respiratory and systemic symptoms, with high fever as a characteristic feature.<sup>21</sup> While influenza A and B are the most common causes of this influenzalike illness (ILI), other pathogens such as influenza C, parainfluenza, respiratory syncytial virus (RSV), and *Mycoplasma pneumoniae* can also cause it.<sup>21</sup>

Different strains have been found to elicit different clinical features. Influenza A H3N2 infection has been found to be more severe than H1N1 or B in terms of fever, leukopenia, or C-reactive protein, whereas gastrointestinal symptoms seem to be more common in influenza B.<sup>22</sup> However, another study found similar clinical manifestations and outcomes among adults with influenza A and those with influenza B.<sup>23</sup> Wie et al described that leukopenia or thrombocytopenia was found to occur more often in patients with influenza B; however, the rate of hospitalization and hospital length of stay (LOS) were found to be higher in those with influenza A (H3N2). In addition, the proportion of males to females and of elderly population were significantly higher for patients with influenza A compared with those with influenza B.<sup>24</sup>

### Viral Pneumonia

Viral pneumonia is the most common complication of influenza infection. A study in 2015 looked at risk factors for developing pneumonia from influenza infection. Among 4,765 adults hospitalized with influenza, 1,392 (29%) had pneumonia. In multivariable analysis, factors associated with pneumonia were age  $\geq 75$  years, Caucasian race, nursing home residence, chronic lung disease, immunosuppression, and asthma. Patients with pneumonia were significantly more likely to require ICU admission (27 vs. 10%), require invasive mechanical ventilation (MV; 18 vs. 5%), and have an increased risk of death (9 vs. 2%).<sup>25</sup> Influenza-associated pneumonia may be either primary viral influenza pneumonia, secondary bacterial pneumonia, or influenza–bacterial coinfection. Patients with pneu-

monia are significantly more likely to have a hospital LOS greater than 1 week, require ICU admission, require MV, and have an increased risk of death.<sup>25</sup>

Among patients with viral pneumonia, factors independently associated with a poor outcome (defined as ICU admission, the need for MV, or death) included nursing home residence, chronic lung disease, cardiovascular disease, renal disease, and immunosuppression. Of note, older age was found as a protective factor among patients hospitalized with pneumonia.<sup>25</sup>

### Risk Factors for Severe Influenza Infection

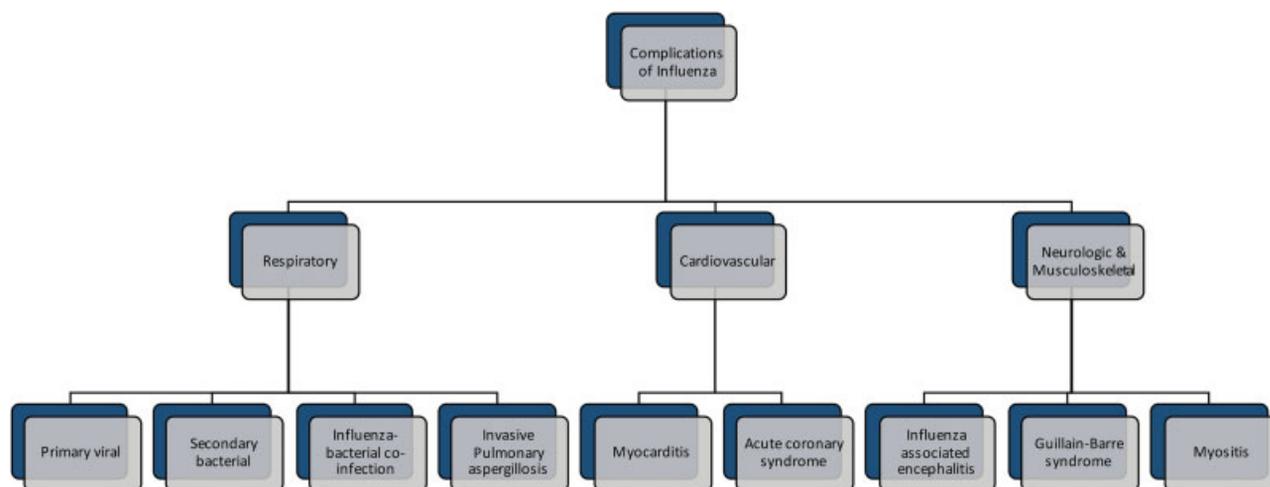
Coleman et al examined the risk factors for serious outcomes associated with influenza illness in high-income countries (HICs) versus low- and middle-income countries (LMICs). They found that patients more likely to suffer severe outcomes (ICU admission, and/or death) were more vulnerable populations such as those affected with comorbidities (malignancies, immune-suppressing conditions, and renal, cardiac, and lung diseases including tuberculosis).<sup>26</sup> Another important risk factor is pregnancy. Pregnant women in LMICs were at 66 percent increased risk of severe outcome compared with other patients with influenza; however, there was no increased risk for pregnant women in HICs. Similarly, patients with HIV were not at an increased risk of severe outcome in HICs; however, they were at an increased risk of LMICs.<sup>26</sup>

### Coinfection

While treatment of CAP has traditionally focused on bacterial etiology, more recent research has indicated that viruses may be involved in 15 to 30% of CAP.<sup>27–29</sup> Rapid diagnostic testing is thus of vital importance in identifying the offending pathogen, initiating targeted treatment, and preventing the inappropriate use of antibiotics. Systematic reviews and meta-analyses found that respiratory viruses are detected in approximately 22% of CAP patients.<sup>30,31</sup> Influenza is consistently the most common viral pathogen identified. There was a trend toward lower identification of viral pathogens in studies published from 2001 to 2009 as opposed to studies published after 2010.<sup>30</sup> In this study, the viruses most commonly identified in European adult patients with CAP from more to less frequent were influenza (A & B), rhinovirus, coronavirus, parainfluenza, human metapneumovirus, RSV, and adenovirus.

### Bacterial Coinfection

The frequency of bacterial coinfection in patients with influenza was reported as being between 11 and 35%. *Streptococcus pneumoniae* and *S. aureus* were the most common pathogens accounting for 35 and 28% of identified coinfecting bacteria, respectively. Influenza infection has been associated with 11 to 14% of pneumococcal pneumonia during influenza season and 5 to 6% overall.<sup>32</sup> In addition, Grabowska et al found that 6 to 10% of cases of invasive pneumococcal disease were associated with influenza per year or 12 to 20% per influenza season.<sup>33</sup> Several other pathogens such as nonfermenting gram-negative bacilli have also been identified as causing coinfections.<sup>34</sup> There



**Fig. 1** Complication of influenza infection in patients admitted to hospital settings.

are several reasons for propensity to bacterial coinfection that are complex and not yet fully explained (► **Fig. 1**). There appear to be organism-specific interactions with *S. aureus* and *S. pneumoniae* that cause a higher rate of infection with these bacteria.<sup>16</sup> A recent multicenter study by Martin-Loeches et al, which included almost 3,000 critically ill patients, has shown that coinfections are occurring more frequently since 2009. Coinfection was more likely to occur in older and immunosuppressed patients. In addition, coinfection was an independent risk factor for ICU mortality, 28-day mortality, and hospital mortality.<sup>35</sup>

Another recent multicenter study analyzing immunosuppressed patients found that the category of infectious etiology of respiratory failure (influenza, noninfluenza, influenza plus coinfection, and noninfectious) was associated with ICU but not hospital mortality.<sup>36</sup>

### Invasive Pulmonary Aspergillosis

A Spanish group in 2011 reported the first cases of invasive aspergillosis (IA) when patients were admitted to the ICU due to influenza infections.<sup>37</sup> A retrospective multicenter cohort study by Schauvlieghe et al examined the incidence of IA in patients admitted to the ICU with severe influenza. They found that IA was present in 32% (38/117) of immunocompromised patients and 14% (45/315) immunocompetent patients.<sup>38</sup> The incidence of IA was almost equal in patients with influenza A and those with influenza B. In addition, they compared 315 nonimmunocompromised influenza-positive patients with an equal number of nonimmunocompromised influenza-negative patients with severe CAP. They found that influenza was “independently associated with invasive pulmonary aspergillosis.”<sup>38</sup>

### Treatment

Data on the use of NA inhibitors (NAI) in intensive care patients are limited. A meta-analysis by Muthuri et al showed that early initiation ( $\leq 2$  days after symptom onset) of NAI treatment versus late initiation (treatment commenced  $> 2$  days after symptom onset) reduced mortality and requirement of venti-

latory support but did not reduce the incidence of influenza-related pneumonia in patients with influenza A(H1N1)pdm09. They found that among the critically ill patient population, NAI use was associated with a reduction in mortality compared with no therapy (odds ratio [OR]: 0.72; 95% confidence interval [CI]: 0.56–0.94) and that early use of NAIs was associated with a reduction in mortality compared with late initiation of treatment (OR: 0.62; 95% CI: 0.49–0.77).<sup>39</sup>

The impact of early ( $\leq 2$  days of symptom onset) versus late ( $> 2$  days after symptom onset) administration of oseltamivir was also examined by Rodrigo et al. This was a prospective observational study of adult patients admitted to ICU with microbiologically confirmed influenza A during the 2009 influenza season in Spain. The study included 657 patients. In the entire patient population, there was a nonsignificant difference in ICU mortality in patients who received early treatment (EL) versus late treatment (LT) (OR: 1.45; 95% CI: 0.96–2.21).<sup>40</sup>

A further subgroup analysis looked at the 404 patients who required MV. Of these, 385 patients received effective antiviral therapy. ET was initiated in 20.5% of patients ( $n = 79$ ), whereas LT was initiated in 79.5% of patients ( $n = 306$ ). LT compared with ET was associated with increased ICU LOS ( $22.7 \pm 16.7$  vs.  $18.4 \pm 14.2$  days;  $p = 0.03$ ), hospital LOS ( $34.0 \pm 20.3$  vs.  $27.2 \pm 18.2$  days;  $p = 0.001$ ), and MV days ( $17.4 \pm 15.2$  vs.  $14.0 \pm 12.4$ ;  $p = 0.04$ ). ICU mortality was also higher with LT (34.3%) than with ET (21.5%; OR: 1.9; 95% CI: 1.06–3.41). These findings suggest that early oseltamivir administration was associated with improved outcomes in ventilated patients during the 2009 H1N1 pandemic.<sup>40</sup> A study by Lytras et al examined the effect of early oseltamivir treatment on mortality in critically ill patients infected with influenza A/H1N1, A/H2N3, and influenza B over eight seasons from 2010 to 2011 and from 2017 to 2018. This was a cohort study including 1,330 patients, of whom 622 (46.8%) died in the ICU. Among patients with influenza A/H3N2, there was a reduction in mortality observed in the ET group compared with the LT group (33.7 vs. 48.4% respectively;  $p = 0.029$ ). Median LOS in the ICU was also shorter in the ET group (12 vs. 15 days;

$p = 0.003$ ). In this study, no significant effect of early versus late oseltamivir was observed for influenza A/H1N1 or influenza B.<sup>41</sup>

Concerns regarding the absorption of oseltamivir in critically ill patients have led to several studies of the use of high-dose oseltamivir. The standard dose of 75 mg twice daily was found to achieve similar plasma levels in critically ill patients compared with ambulatory patients. These concentrations were far in excess of concentrations required to maximally inhibit NA activity of the virus.<sup>42</sup> High-dose oseltamivir has also been shown to achieve similar effects to standard dose oseltamivir in terms of mortality and viral RNA.<sup>43</sup> While 5 days of oseltamivir has been the standard duration of therapy in ambulatory patients, it has been suggested that therapy should be continued in patients who remain in a critical state after 5 days of treatment.<sup>44,45</sup> The intravenous NAI, peramivir, has been shown to be as effective as oral oseltamivir in terms of mortality and length ICU stay.<sup>46</sup> It could thus be considered as an alternative in those unable to take oral oseltamivir.

Other potential treatments have been investigated. A systematic review and meta-analysis by Mair-Jenkins et al examined studies on convalescent plasma for the treatment of severe acute respiratory infections of viral etiology. It included a post hoc meta-analysis of pooled data from eight comparative studies: two studies on SARS-CoV (severe acute respiratory syndrome-coronavirus) infection, two on influenza A(H1N1) pdm09 infection, one on avian influenza A(H5N1) infection, and three on Spanish influenza A(H1N1) infection. The results from this meta-analysis suggest that convalescent plasma may have an impact on reducing mortality and viral load in patients with severe acute respiratory infections of viral etiology.<sup>44</sup> There have been case reports of a rapid reduction in detectable viral load in patients with influenza A (H5N1) treated with convalescent plasma without significant serious events.<sup>47-49</sup>

A prospective cohort study conducted during the H1N1 2009 pandemic included 93 patients with severe infection requiring intensive care. Twenty patients (21.5%) received convalescent plasma. Mortality in the treatment group was significantly lower (20.0 vs. 54.8%;  $p = 0.01$ ). Respiratory tract viral load, IL-6, IL-10, and TNF- $\alpha$  were also significantly lower in the treatment group.<sup>50</sup>

Different studies have tried to analyze the association of the role of adjuvant immunomodulatory agents for the treatment of severe influenza, including corticosteroids, statins, macrolides, nonimmune intravenous immunoglobulin, N-acetylcysteine, pamidronate, nitazoxanide, chloroquine, antiC5a antibody, IFNs, human mesenchymal stromal cells, mycophenolic acid, peroxisome proliferator-activated receptors agonists, nonsteroidal anti-inflammatory agents, and mesalazine, with the role of plasmapheresis and hemoperfusion as a rescue therapy.<sup>51</sup> While none of these immunomodulatory therapies have shown any benefit, we have to acknowledge that the evidence is unclear due to limited published database on randomized controlled trials (RCTs). In critically ill patients, two of these coadjuvant treatments have gathered most of the attention: macrolides and corticosteroids. The use of macrolides was analyzed in a large cohort of patients with the use of a

propensity score analysis, and their use was not associated with any benefit in critically ill patients.<sup>52</sup>

A Cochrane review (originally published in 2016 followed by updated review in 2019) included 30 studies with 99,224 participants and found that corticosteroid therapy was associated with increased mortality. A similar increase in risk of mortality was seen in a stratified analysis of studies reporting adjusted estimates. An association between corticosteroid therapy and increased mortality was also seen in a pooled analysis of six studies that reported adjusted hazard ratios (HRs) (HR: 1.49; 95% CI: 1.09-2.02;  $I^2 = 69\%$ ). Increased odds of hospital-acquired infection related to corticosteroid therapy were found in a pooled analysis of seven studies (pooled OR: 2.74; 95% CI: 1.51-4.95;  $I^2 = 90\%$ ); all were unadjusted estimates, and the data was graded as of very low certainty. Limitations of the review included inconsistent reporting of variables and low quality of data specific to mortality.<sup>53</sup>

Corticosteroids have been shown in several meta-analyses to be associated with increased mortality.<sup>54-56</sup> As a caveat, it has been suggested that corticosteroids may have been given to the sicker patients in the studies included in these meta-analyses, patients in whom the mortality was going to be higher anyway. The authors of these meta-analyses also concluded that there is a lack of sufficiently powered randomized trials examining the issue.

Regarding extracorporeal life support, the 2009 pandemic saw an increase in frequency of the use of venovenous extracorporeal membrane oxygenation (ECMO) as a rescue therapy in patients with severe acute respiratory distress syndrome (ARDS). A systematic review by Sukhal et al examined the use of ECMO in severe influenza infection. While there is a lack of randomized trials in the study, their results do suggest a benefit from the initiation of ECMO in severe respiratory failure secondary to H1N1 influenza.<sup>57</sup>

## Nonrespiratory Complications

### Cardiovascular Complications

The incidence of myocarditis in patients with influenza may be as high as 10%.<sup>58</sup> It commonly occurs between days 4 and 7 after the onset of influenza symptoms.<sup>59</sup> Myocarditis is diagnosed based on a combination of symptoms, elevated cardiac enzymes, and echocardiographic findings. Myocarditis is not limited to those with severe respiratory manifestations of influenza. Symptoms related to myocarditis, such as chest pain, dyspnea, and syncope, may have been the cause of presentation to hospital in the first instance.<sup>59</sup> The clinical manifestations range from subclinical myocarditis to sudden death, new-onset atrial or ventricular arrhythmias, complete heart block, heart failure, pericardial effusion, cardiac tamponade, and acute myocardial infarction (AMI)-like syndromes.<sup>58,60</sup> The most common complication is congestive heart failure diagnosed by global hypokinesia on echo/MRI (magnetic resonance imaging), which has been reported in 84% (37/44) of patients with influenza-associated myocarditis. The majority (70%; 26/37) of those who had myocarditis-related reduced ejection fraction (ranging from 8 to 50%) experienced resolution

of their systolic function, typically within 20 days of the onset of dysfunction.<sup>60</sup>

Many patients who develop influenza-related myocarditis require advanced cardiac support therapies such as intra-aortic balloon pumps and ECMO. Early diagnosis is paramount, and mortality has been reported as approximately 23%.<sup>60</sup> It is important to note that reduced ejection fraction in the absence of myocarditis has been reported in influenza infection. Right ventricular dysfunction appears to be more common than left ventricular dysfunction and is over and above what would normally be expected in patients with ARDS.<sup>61</sup>

A meta-analysis of case-control studies by Barnes et al found that recent influenza infection, ILI, or respiratory tract infection was significantly more likely in AMI cases (pooled OR: 2.01; 95% CI: 1.47–2.76). In addition, influenza vaccination was negatively associated with AMI (pooled OR: 0.71; 95% CI: 0.56–0.91).<sup>49</sup> These findings are in keeping with other studies on the association between influenza and AMI,<sup>62,63</sup> and influenza vaccination and AMI.<sup>64,65</sup> The pathogenesis may be due to several mechanisms, including increased coronary and systemic inflammatory activity that drives procoagulant processes, dominant prothrombotic conditions, increased biomechanical stress on coronary arteries, variations in the coronary arterial tone, disturbed hemodynamic hemostasis, and altered metabolic balance.<sup>66</sup>

Other less common cardiovascular complications are dysrhythmias and pericarditis. The most commonly reported cardiac arrhythmias associated with influenza are atrioventricular conduction block and ventricular fibrillation. These are usually due to underlying fulminant myocarditis.<sup>58</sup> Although pericarditis is a recognized complication of influenza infection, it is often mild and uncomplicated.<sup>58</sup>

### Neurologic Complications

Influenza-associated encephalitis or encephalopathy is a syndrome characterized by an impaired level of consciousness occurring within a few days of influenza infection. The most common neurologic symptoms are confusion and seizures. MRI and computed tomography (CT) commonly produce abnormal findings, with lesions being located throughout the brain with no characteristic patterns or areas of focus.<sup>67</sup>

While the most common associated agents in Guillain-Barre's syndrome (GBS) are *Campylobacter jejuni*, *M. pneumoniae*, and EBV, 60 to 70% of cases of GBS do not have a clear etiology identified.<sup>60</sup> Influenza virus has been proposed as an important and underrecognized cause of GBS. Numerous studies have found a significantly increased risk of GBS in the months following influenza infection.<sup>68,69</sup>

In addition to neurologic complications, elevation in creatine kinase (CK) has been suggested as a biomarker of the severity of influenza infection. In a study by Borgatta et al of cases of influenza A pH1N1 infection in 2009, CK  $\geq$  500 UI/L was associated with greater renal dysfunction and requirement of renal replacement therapy. Increase of CK  $\geq$  1,000 UI/L was associated with greater intubation risk, longer duration

of MV, and 5 extra days of ICU and hospital LOS.<sup>70</sup> Rhabdomyolysis, although rare, has been reported in association with influenza infection.<sup>60</sup>

### Mortality

The hospitalization fatality risk, defined as the probability of death among H1N1pdm09 patients who required hospitalization for medical reasons, was examined in a systematic review and meta-analysis by Wong et al. Crude estimates of the HFR ranged from 0 to 52%. There was, however, substantial heterogeneity of studies. Higher estimates came from tertiary-care referral hospitals in countries with lower gross domestic products (GDPs). Countries with lower GDPs were hypothesized to have had higher thresholds for hospital admission and ICU treatment. The hospitalized cases may have been more severe than in countries with higher GDPs. The risk of death would thus have been higher. In wealthy countries, the estimate was 1 to 3% in all settings.<sup>71</sup> A systematic review by Khandaker et al found a confirmed case fatality rate of 1.1% in HICs and 4.6% in upper- and lower-middle income countries during the pandemic of 2009.<sup>72</sup> The mortality rate for critically ill patients with severe influenza requiring admission to the ICU during the 2009 to 2010 pandemic was approximately 26% in HICs, 37% in upper-middle income countries, and 58% in lower-middle income countries.<sup>73</sup>

### Other Severe Nosocomial Viral Infection in Immunocompromised Patients

Immunoparalysis following the initial proinflammatory response to physiological insult (sepsis, trauma, etc.) is frequent in nonimmunocompromised ICU patients.<sup>74</sup> One of the consequences of this immunoparalysis is the reactivation of latent viruses, with herpesviridae (mostly HSV, CMV, and EBV) being the most frequent.

### Herpes Simplex Virus

Numerous studies have evaluated HSV reactivation in ICU patients<sup>75–79</sup> (–Table 1). To summarize these studies, HSV reactivation starts in the oropharyngeal tract in 20 to 50% of ICU patients, 3 to 5 days after ICU admission, followed by a descending lower respiratory tract colonization in 20 to 65% of mechanically ventilated patients, after a median of 7 days of MV and with a peak of virus load 12 days after MV start.<sup>80</sup> In some patients, a true lung infection (HSV bronchopneumonitis) can occur after a median of 14 days of MV; in a study evaluating 201 patients with prolonged (>4 days) MV, Luyt et al found that 20% of them had HSV bronchopneumonitis with cytological and/or histological signs of deep lung infection.<sup>76</sup> Distinguishing HSV lung reactivation from infection may be difficult; indeed, lung infection is defined by clinical signs, presence of HSV, and cytological/histological criteria, that is, HSV-specific nuclear inclusions on cells collected during bronchoalveolar lavage (BAL).<sup>76</sup> However, this technique is difficult to implement and may be subjective. Virus load in BAL fluid, with a cutoff set at  $10^5$  copies/mL, may be a good alternative.<sup>76,78,81</sup>

**Table 1** Main studies having evaluated HSV, CMV, and EBV reactivation in ICU patients

Study	Population	Virus reactivation frequency, N (%)	Method of detection
<b>HSV reactivation</b>			
Bruynseels et al, 2003 <sup>75</sup>	764 patients, 361 of them receiving MV	169 /764 (22%) in the throat 58/361 (19%) in distal airways	Viral culture
Ong et al, 2004 <sup>77</sup>	393 receiving MV	106 (27%)	PCR
Luyt et al, 2007 <sup>76</sup>	201 patients ventilated for >4 d, suspected of having developed VAP	109 (54%) in the throat 129 (64%) in distal airways	PCR, viral culture
Linszen et al, 2008 <sup>78</sup>	260 patients suspected of having developed VAP	99 (32%) in distal airways	PCR
Costa et al, 2012 <sup>79</sup>	127 patients suspected of having developed VAP	38 (31%) in distal airways	PCR
<b>CMV blood reactivation</b>			
Jaber et al, 2005 <sup>85</sup>	237 patients with fever	40 (17%)	pp65 antigen
Limaye et al, 2008 <sup>86</sup>	120 CMV-seropositive patients	39 (33%)	PCR
Chiche et al, 2009 <sup>87</sup>	242 mechanically ventilated patients	33 (14%)	pp65 antigen
Limaye et al, 2017 <sup>88</sup>	72 CMV-seropositive patients included in the placebo arm	28 (39%)	PCR
<b>CMV lung disease</b>			
Papazian et al, 1996 <sup>89</sup>	86 patients with acute respiratory failure or VAP	25 (29%)	Histology (autopsy or biopsy)
Papazian et al, 2007 <sup>90</sup>	100 patients with unexplained ARDS	30 (30%)	Histology (biopsy)
Chiche et al, 2009 <sup>87</sup>	242 mechanically ventilated patients	11 (5%)	Viral culture
<b>EBV reactivation</b>			
Tachikawa et al, 2014 <sup>93</sup>	87 patients with unexplained ARDS	16 (18%) in BAL fluid	PCR in BAL fluid
Libert et al, 2015 <sup>94</sup>	86 EBV-seropositive patients with ICU LOS $\geq$ 5 days	61 (71%) EBV detection in the blood	PCR in blood
Ong et al, 2017 <sup>95</sup>	329 immunocompetent patients with septic shock	157 (48%) EBV detection in the blood	PCR in blood

Abbreviations: ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; PCR, polymerase chain reaction; VAP, ventilator-associated pneumonia.

HSV reactivation is associated with a poor outcome; a meta-analysis showed that HSV reactivation was associated with mortality (OR: 1.8; 95% CI: 1.2–2.6)<sup>82</sup>; however, the exact significance of HSV reactivation (i.e., bystander or true pathogen with its own morbidity/mortality) remains to be determined. To date, only one small randomized controlled study using prophylactic acyclovir failed to demonstrate any clinical beneficial effect of antiviral treatment.<sup>83</sup> One retrospective study found an improvement in mortality in HSV carriers having received acyclovir,<sup>84</sup> and one prospective study failed to show any beneficial effect of acyclovir in patients with HSV bronchopneumonitis.<sup>76</sup>

### Cytomegalovirus

Blood and/or lung CMV reactivation may occur in ICU patients<sup>85–90</sup> (–Table 1). Blood CMV reactivation occurs in one-third of CMV-seropositive ICU patients after a median of 4 to 12 days after admission. Lung CMV reactivation/infection is less frequent, occurring in 5% of mechanically ventilated patients<sup>87</sup>; but the frequency can reach 30% in patients with

acute lung injury without an obvious cause.<sup>89,90</sup> A recent meta-analysis showed that 27% of ICU may experience CMV reactivation, whatever be the site (blood or lung) of reactivation.<sup>91</sup> Although CMV blood reactivation is associated with poor prognosis,<sup>82,91</sup> no study has evaluated the relationship between CMV blood reactivation and CMV disease (i.e., organ involvement). CMV lung disease has been almost exclusively diagnosed using histology on lung biopsies or autopsies,<sup>89,90</sup> whereas the use of cytology on BAL-collected cells (looking for CMV-specific inclusions) or quantitative polymerase chain reaction (PCR) has never been investigated.

Like HSV, CMV reactivation is associated with a poor outcome; a recent meta-analysis showed that CMV reactivation in nonimmunocompromised patients was associated with mortality (OR: 1.72; 95% CI: 1.04–2.85).<sup>91</sup> Moreover, Limaye et al found that CMV virus load was associated with mortality: the higher the virus load, the higher the mortality.<sup>86</sup> However, again, the exact significance of CMV reactivation is not known; it could be a marker of severity (bystander) or a pathogen with true morbidity and/or mortality.

Two randomized controlled trials evaluating the effectiveness of prophylactic anti-CMV treatment in CMV-positive ICU patients were recently published.<sup>88,92</sup> The first one evaluated prophylactic valganciclovir or valacyclovir, as compared with a placebo, to decrease CMV reactivation. While inclusions in the valacyclovir arm were prematurely stopped due to unexplained increased mortality, patients treated with valganciclovir had less CMV reactivation than, but similar outcomes to, placebo-treated patients.<sup>92</sup> In the second one, a double-blind, placebo-controlled trial, the authors evaluated prophylactic ganciclovir to reduce IL-6 level (measured 14 days after randomization). Although ganciclovir failed to reduce IL-6 level at day 14, as compared with placebo, there was a trend toward increased ventilator-free days at day 28 in patients having received ganciclovir, but with similar mortality.<sup>88</sup>

### Epstein-Barr Virus

Recently, some authors investigated the frequency of EBV DNA detection in BAL fluid<sup>93</sup> or in the blood<sup>94,95</sup> using PCR (► **Table 1**). They found that EBV DNA detection is frequent in ICU patients and seems to be associated with mortality.<sup>94,95</sup> Again, the exact significance of EBV detection in ICU patients has to be determined, and thus to consider a specific treatment against EBV in ICU patients with EBV DNA detection is to date premature.

In summary, herpesviridae reactivations are frequent in ICU patients and associated with mortality. However, the exact significance of herpesviridae reactivation is poorly understood. In some cases, it is associated with a true disease; but in some cases, the relationship between viral reactivation and viral disease is not established. In these latter cases, whereas a specific antiviral treatment may improve outcome remains to be determined. To date, neither prophylactic acyclovir to prevent HSV reactivation nor prophylactic ganciclovir to prevent CMV reactivation can be recommended; preemptive treatment with acyclovir in patients with oropharyngeal HSV reactivation or ganciclovir in patients with CMV blood reactivation is under investigation (PTH [Preemptive Treatment for Herpesviridae] study, Clinical Trials n° NCT02152358). Curative treatment of HSV bronchopneumonitis or CMV lung disease is based on expert opinions in patients with either cytological/histological proofs of lung involvement, high viral load, or specific clinical and biological patterns suggestive of CMV.<sup>96,97</sup>

### Summary

Patients in ICU are at risk of viral infections. In immunocompetent patients, the most common viral infections are respiratory, and influenza should be considered in patients with severe respiratory failure being admitted to the ICU. Seasonality and coinfection are two important features when considering influenza as a pathogen in critically ill patients.

Viral infections are more frequent in immunosuppressed patients. Solid organ and hematopoietic stem cell transplant recipients, as well as those receiving chemotherapy for a malignant hematological disease are clearly predisposed to a variety of viral infections, both common and opportunistic.

The patient may have acquired these infections from the community, the donor organ (donor-derived infections), and/or reactivation of an endogenous latent virus. HSV, especially CMV and EBV, is among the most common of the opportunistic viral pathogens affecting these patients in addition to respiratory viruses. In recent years, several studies have found that these opportunistic infections can also cause the development of an infection in immunocompetent patients with some transient degree of induced immunosuppression.

### Conflict of Interest

None.

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