Severe influenza: overview in critically ill patients

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Purpose of review
Overview of influenza infection, focusing on outcome and complications in critically ill patients. We also discuss relevant elements in immunopathogenesis and their role as predictors of severity.

Recent findings
Pandemic influenza A (H1N1) virus circulates seasonally and remains the predominant subtype among intensive care patients. Mortality in acute respiratory failure (ARF) is around 20%, independent of influenza subtypes. During severe infection, the imbalance between pro-inflammatory and anti-inflammatory molecules, such as Th1 and Th17 cytokines, is associated with complicated infections and mortality. Primary viral pneumonia presents in more than 70% of ICU influenza patients and more than 50% develop acute respiratory distress syndrome. Bacterial secondary infection occurs in 20% of severe cases and *Streptococcus pneumoniae* and *Staphylococcus aureus* remain the prevalent pathogens. Myocarditis and late-onset cardiovascular complications are associated with mortality. Antiviral therapy within 48 h after onset, avoidance of corticosteroids and rescue therapies for ARF or myocarditis, such as extracorporeal membrane oxygenation, improve survival.

Summary
The present review summarizes current knowledge on pathogenesis and clinical manifestations of severe influenza. Immunological dysfunction during viral infection correlates with severity and mortality among ICU patients. A theranostics strategy should be implemented to improve outcomes.

Keywords
acute respiratory failure, myocarditis, primary viral pneumonia, secondary pneumonia, severe acute respiratory infection

INTRODUCTION

Influenza is responsible for up to 650 000 annual deaths worldwide [1]. Although mostly a self-limited disease, 5–10% of hospitalized patients with influenza required ICU admission mainly because of acute respiratory failure (ARF) [2]. Asthma and croup are more frequent in chronic obstructive pulmonary disease (COPD) and children [2,3]. Among them, the mortality rate is around 20% [2,4,5]. Diagnosis in ARF should be based on PCR or arrays of lower respiratory tract specimens; negative nasal swab does not rule out the diagnosis [6▪]. Influenza vaccination rates remain suboptimal [7].

The aim of this study is to understand outcome changes during the last influenza seasons according to different types and subtypes of influenza; to highlight the clinical manifestations and the risk factors associated with complicated disease; finally, to know the immunopathology of infection and which are the therapeutic strategies used in ICU to treat patients with severe influenza.

EPIDEMIOLOGY AND ESTIMATING THE BURDEN OF SEVERE INFLUENZA

In Europe, the median annual mortality was estimated to be 44 774, representing 11% of the global disease burden [1] and hospitalizations were higher for children less than 5 years and adults at least 65 years [8]. Among hospitalized cases, 34.1% resulted in ICU admissions and 12.1% in death, with older adults showing the highest hospital fatality rate (18%) [8]. During this period, the pandemic

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KEY POINTS

- Seasonal influenza infection in ICU is responsible for a 20% mortality with primary pneumonia being present in more than 70% of ICU admissions.
- Host immune factors, such as TH1 and TH17 cytokine production, can impact the severity and mortality among ICU patients with influenza.
- Secondary pneumonia adds to severity of illness and ICU admission in 20% of cases; *Streptococcus pneumoniae* and *Staphylococcus aureus* remain the most prevalent coinfecting pathogens over the years.
- Extrapulmonary complications, including myocarditis, can occur during the first week of infection without respiratory symptoms in healthy, young patients.
- Antiviral administration within 48 h of onset and vaccination represent the main strategies that improve outcomes.

influenza A (H1N1)pdm09 was the predominant subtype, circulating in the 2010/2011, 2013/2014, and 2015/2016 influenza seasons [8]. The 2016/2017 and 2017/2018 seasons were dominated by the A (H3N2) subtype and type B (Yamagata lineage), respectively [9]. Since 2011, the WHO and ECDC advocate a syndromic approach to monitor trends of respiratory infections through the use of influenza-like illness (ILI) and severe acute respiratory infection (SARI) case definitions (Table 1). Through integration of virological data, it is possible to understand disease burden and the impact of influenza in relation to other diseases [10]. Although ILI monitoring is well implemented in the outpatient setting, surveillance of SARI that requires hospitalization is not widely used [11] and most countries adopt a strategy of monitoring hospitalized cases that are laboratory-confirmed or have a suspected diagnosis of influenza. In the Netherlands, 8–17 SARI ICU admissions occurred per 1000 cases of ILI in primary care from 2007 to 2016, with peak weekly incidence of SARI varying between 101 and 188 in the 2013/2014 and 2012/2012 epidemics, respectively [11]. The great variability in the ratio of ILI to SARI cases between epidemics shows that ILI trends in the outpatient setting do not predict ICU burden of disease. In this study, less than half of patients were screened for respiratory viruses, although a codified diagnosis of viral pneumonia was present in 4.7%. The ILI case definition is also a useful tool to prompt influenza screening in critically ill patients admitted with SARI. In a Spanish cohort of 163 patients with SARI admitted to the ICU over 3 influenza seasons (2011–2014), 40% presented with ILI, and influenza infection was almost three times more frequent than in non-ILI patients [12].

Table 1. The WHO surveillance case definition for influenza-like illness and severe acute respiratory infection [10]

Influenza-like illness
An acute respiratory infection with:
measured fever of ≥38°C;
and cough;
with onset within the last 10 days.
Severe acute respiratory infection
An acute respiratory infection with:
history of fever or measured fever of ≥38°C;
and cough;
with onset within the last 10 days;
and requires hospitalization.

DESCRIPTION OF OUTCOMES OVER THE PAST DECADE

The INSIGHT Influenza Study Group described the outcomes of an international cohort of 1398 hospitalized patients with influenza 2009–2015, which included 15.2% patients enrolled at the ICU [4]. Patients with influenza A (H1N1)pdm09 were more likely to be enrolled from the ICU compared to A (H3N2) and B (20.3, 11.3, and 9.8%, respectively), but did not experience worse outcomes at 60 days (Table 2). Even when comparing a composite outcome of death, extended hospitalization, or mechanical ventilation, results did not differ significantly (48.3, 43.1, and 45.0%, respectively). Patients with influenza A (H1N1)pdm09 were younger than those with influenza A (H3N2) and B, with a respective proportion of adults greater than 65 years of age of 11.5, 55.1, and 36.4%; they also had fewer comorbidities overall. Similarly, in other studies of patients with influenza A (H1N1)pdm09, the median patient age was 50 years and mortality rates were comparable across study periods (about 20%) [5,14▪]. *Martínez et al.* [13▪] described similar outcomes over six influenza seasons (2010–2016) and also found no difference in presence of multiorgan failure at ICU admission (21.1–25.3%) and hospital length of stay (26–27 days). One study in two centers in Netherlands [2] reported comparatively higher ICU mortality and need for mechanical ventilation (Table 2). This could be because of the hospital's referral function, since the 2015/2016 seasonal epidemic did not result in increased mortality in the Netherlands. In order to improve at-risk patient selection, most studies attempt to identify risk factors of complications and poor outcome. Risk factors for complications identified in the past

Table 2. Summary of key studies describing severe hospitalized influenza cases in the post-pandemic period

Reference	Country	Period	*N*	Influenza type/ subtype	Intensive Care Unit								Hospital deaths (%)
					Admission (%)	Age (mean (SD), years)	Any comorbidity (%)	Immuno-suppression (%)	MV (%)	Antiviral (%)	Vaccination in ≤ 12m (%)	Deaths (%)	
Dwyer *et al.* [4]	International	2009–2015	1398	A (H1N1)p	20.3	47 ± 3.7	50.8	15.4	–	84.6	19.0	22.1	7.1
				A (H3N2)	11.3	66 ± 4.2	83.3	21.7	–	83.3	46.3	23.7	5.0
				B	9.8	51 ± 5.5	59.1	13.6	–	81.8	31.2	38.1	7.3
Martinez *et al.* [13▪]	Spain	2010–2016	1726	A (H1N1)p	39.6	56.5 ± 14.4	74.3	25.4	–	95.1	12.9	–	13.6
				A (H3N2)	26.0	64.9 ± 15.6	82.2	15.8	–	88.9	31.7	–	14.4
				B	30.9	61.2 ± 16.2	74.7	25.3	–	86.1	23.0	–	12.8
Garnacho-Montero *et al.* [14▪]	Spain	2009–2015	1899	A (H1N1)p	100	51 ± 3.7	–	12.5	63.6	97.7	–	23.6	–
Marin-Corral *et al.* [5]	Spain	2009–2011	1337	A (H1N1)p	100	46 ± 13	72.1	18.0	71.7	–	1.7	20.7	–
		2013–2015	868	A (H1N1)p	100	55 ± 14	76.0	17.9	66.5	–	11.1	24.2	–
Hernu *et al.* [15]	France	2008–2013	201	A (85%)	100	63 ± 16	91	–	89	73	12	26.4	–
				A (H1N1)p (50%)									
				B (15%)									
Beumer *et al.* [2]	Netherlands	2015–2016	199	A (71%)	23	53 ± 22	–	62.2[a]	97.8	84.4	–	37.8	9
				B (29%)									

A (H1N1)p, pandemic influenza A (H1N1) virus; MV, mechanical ventilation.
[a]Includes diabetes mellitus and recent use of steroids or other immunosuppressive drugs.

include the extremes of age (<5 and ≥65 years), chronic underlying medical conditions, extreme obesity (BMI ≥40 kg/m^2), and being a resident in a nursing home [16]. Pregnant women, particularly in the last trimester, have a higher risk of ICU admission and complicated infection compared to nonpregnant women of childbearing age; prompt treatment with oseltamivir is indicated and vaccination is recommended in all pregnant women [17]. In one study, seasonal influenza vaccination was associated with reduced ICU admission in patients with influenza A [13▪], but the statistical power was low to detect any association in type B or A subtypes. *Beumer et al.* [2] found that the presence of dyspnea and particular comorbidities (obstructive sleep apnea and history of myocardial infarction) were associated with ICU admission. Age 50–65 years and influenza type A were also predictors of ICU admission, but this could be a reflection of the predominance of influenza A (H1N1)pdm09 in the 2015/2016 season in the Netherlands. Factors associated with ICU mortality were age at least 65 years, chronic diseases (cardiovascular, liver, and renal), and immune deficiency [13▪]. Other previously demonstrated risk factors for increased ICU mortality include stage 3 acute kidney injury (AKI) and elevation of creatine kinase at least 300 UI/L [18]. Another study [14▪] of patients with influenza (H1N1)pdm09 also found immunosuppression to be associated with increased ICU mortality (49.6 vs. 19.9%), particularly in hematological disease (mortality of 51%). When comparing all the immunosuppressed with nonimmunosuppressed patients, factors independently associated with increased mortality were higher median SOFA score (9 vs. 6) use of vasopressors, stage 3 of AKI and use of corticosteroids.

THE ROLE OF THE HOST IMMUNE RESPONSE

The inflammatory response to influenza and the mechanisms by which severe disease develops are complex and only partially understood. Viral RNAs are recognized by infected cells as pathogen-associated molecular pattern (PAMPs) by pathogen recognition receptors (PRRs) and initiate a downstream of cellular and humoral responses, including a cytokine storm [19]. The primary wave of cytokines includes type I interferon (IFNs) release, which upregulate the expression of various IFN-stimulated genes and induce a downstream of antiviral responses and inflammatory cytokines by innate immune cells, such as dendritic cells, macrophages, neutrophils, and monocytes [19]. This initial phase determines much of the clinical course and outcome of disease, with higher levels of viral replication promoting more inflammation in the setting of reduced or no preexisting immunity as seen in the very young and the elderly [20▪]. Depending on the amount of virus and inflammation after this phase, the adaptive immune response consisting of different subsets of T cells and innate lymphoid cells promotes viral clearance and tissue repair by secreting secondary cytokines, such as IFNγ, interleukin (IL)-10, and IL-5 [19,20▪]. However, patients with severe pneumonia have heightened pro-inflammatory T-cell responses. T helper (Th) 17 and Th1 cytokines were exclusively found in hospitalized patients and were not present in mild disease [21]. Th17 cytokines IL-6 and IL-8 levels also correlated inversely with alveolar O_2 pressure in hospitalized and critically ill patients, respectively [21]. At the same time, Th17 cytokine IL-17 had a protective effect in severe pandemic influenza, whereas granulocyte-colony stimulating factor (G-CSF) was a risk factor for mortality [22]. G-CSF levels correlated negatively with IL-17, supporting a potential inhibitory function on IL-17 secretion and indicating the existence of an imbalance in pro- and anti-inflammatory Th17 responses in severe disease. Furthermore, STAT1, a transcription factor involved in interferon signaling, plays a detrimental role in influenza by controlling the magnitude of Th17 response [23]. STAT1 knockout mice had lesser bacterial superinfection and better outcomes compared to controls, and lymphocytes showed increased Th17 immune activation, suggesting that dysregulated Th17 responses may also contribute to respiratory bacterial superinfection. The implications of the immune response in disease severity and mortality provide the landscape for interventions focusing on modulation of inflammatory response, such as an adjunctive drug that stimulates IL-17 production. At the same time, the response to therapy can be assessed by measuring the levels of the target molecules, allowing for a tailored treatment plan. This approach, called theranostics, follows the oncology model and should be used to design clinical trials [24▪].

PRIMARY VIRAL PNEUMONIA

Primary viral pneumonia is characterized by progression of respiratory symptoms after 2 to 8 days of disease onset. Presenting symptoms include worsening dyspnea, hypoxemia, and bilateral diffuse opacities on chest radiography [25]. Patients are admitted to the ICU because of respiratory distress in more than 70% of cases [4,15]. *Martínez et al.* [13▪] found that primary viral pneumonia was present in

75.8% of ICU admitted influenza infections during 2010–2016. Furthermore, patients with influenza A (H1N1)pdm09 had a higher tendency to develop primary viral pneumonia compared to influenza A (H3N2) and B (80.7, 72.3, and 74.7%, respectively), although differences were not significant. ARDS developed in 57.5% of patients overall, with no differences between viral types/subtypes, which was similar to the rate reported (56%) in a French cohort [15].

Treatment with oseltamivir within 48 h of disease onset to stop viral replication was demonstrated to improve survival [15] and is considered standard of care in the ICU. Conversely, corticosteroid use in the setting of acute respiratory failure or ARDS because of primary viral pneumonia is to be avoided as it is associated with increased mortality [26▪]. High-flow nasal cannula O_2 therapy was used successfully in 9/35 (45%) patients with influenza (H1N1)pdm09 unable to maintain adequate pulse oximetry with conventional O2 therapy [27]. This may be an effective modality when used early, particularly in a subset of patients with asthma or COPD. However, more than 60% of patients require mechanical ventilation (Table 2). Protective lung ventilation is the current standard of care in patients with acute lung injury/ARDS because of the evidence that it decreases mortality. Noninvasive ventilation (NIV) is not recommended in severe viral pneumonia because of high failure rates of more than 60% [5]. Between 4 and 7% of patients require ECMO support because of refractory hypoxemia [2,15]. A systematic review and meta-analysis [28] of ECMO in patients with influenza mainly during the 2009 pandemic demonstrated an overall pooled mortality of 37.1%. Given the lack of large prospective randomized trials, current evidence suggests that ECMO should be offered as rescue therapy in carefully selected patients with influenza with refractory respiratory failure, ideally as part of institutional algorithm [29].

SECONDARY PNEUMONIA

The exact incidence and the clinical impact of pulmonary bacterial coinfection in severe influenza are difficult to estimate because of the presence of heterogeneity in studies. Confounders such as diagnostic and microbiological methodologies, different categories of patients, different definitions of coinfection, influenza seasonality, and overlap in symptoms limit the generalization of the results.

Among critical patients with influenza, bacterial coinfection varied between 11 and 30% worldwide in the pandemic [30,31] particularly in fatal cases [32]. Since then, coinfection has been poorly reported but ranges around 20% in the majority of cases [5,32–34].

Streptococcus pneumoniae is the most prevalent coinfecting pathogen, complicating 26% of overall severe influenza infections and more than 50% of the pandemic cases in Europe [32]. During the latest influenza seasons, the incidence of *S. pneumoniae* secondary infection has been reduced [2] (Table 3). In the United States, *Staphylococcus aureus* is the prevalent pathogen stably reported around 30% of critical influenza patients [31,34]. Finally, *Streptococcus pyogenes* and *Haemophilus influenzae* are isolated in a minority of cases (<5%) in pandemic and post pandemic cohorts [35] (Table 3). Bacterial coinfection is clearly associated with severe illness, development of septic shock [33], and consequent ICU admission with longer duration of mechanical ventilation and resource allocation compared to no coinfected influenza patients [31,34,36]. Influenza-related mortality has not been changed over the years since the pandemic [5] and occurs in patients with secondary pneumonia in around 30% of cases [36]. However, the real impact of coinfection on outcome is difficult to estimate because of heterogeneity and confounders among studies. Comorbidities, such as older age, immunosuppressed status, and steroid therapy [14▪] together with high severity score index (APACHE II, SOFA) are associated with higher mortality among patients with severe influenza, and represent a risk

Table 3. Incidence of bacterial co-infection among 2009 Pandemic and post-Pandemic period

	2009 Pandemic		Post-pandemic		
	EU Martin-Loeches *et al.* [30]	**US Rice *et al.* [31]**	**EU Beumer *et al.* [2]**	**US Shah *et al.* [34]**	**China Teng *et al.* [33]**
S. pneumoniae	55% (62/113)	11% (17/154)	7% (3/45)	5.4% (7/129)	44% (18/41)
S. aureus	8% (9/113)	31% (47/154)	11% (5/45)	36,5% (47/129)	27% (11/41)
P. aeruginosa	8% (9/113)	ND	2,2% (1/45)	14% (18/129)	5% (2/41)
S. pyogenes	5.3% (6/113)	3% (4/154)	2,2% (1/45)	1,6% (2/129)	ND
H. influenzae	2.6% (3/113)	ND	2,2% (1/45)	2.3% (3/129)	7.3% (3/41)

EU, European Union; ND, no data; US, United States of America.

factor for co/secondary infections [37]. Even after adjustment for confounding factors, coinfection is significantly associated with mortality in only a few studies, with an odds ratio or adjusted hazard ratio range from 2.2 to 3 [33,34]. In these studies, *S. aureus* was the prevalent pathogen isolated, but the correlation with poor outcome is observed in only one study [31]. Finally, the delay of antiviral therapy has been observed especially in coinfected patients [34] and it emphasized that early oseltamivir therapy is a protective factor for influenza outcome, including in mixed infections [38].

Influenza-associated Aspergillosis (IAA) is a secondary complication in subjects with lymphocytopenia [39,40]. IAA has been described mainly in the setting of severe influenza A infection, with an increasing trend [40] and mortality rate around 60% [41,42]. IAA can occur in previously healthy patients, suggesting influenza status as an independent risk factor in critically ill patients [40]. In this scenario, only the administration of steroids has been associated with IAA [41] and ICU mortality [14▪,43]. Diagnosis of proven invasive pulmonary aspergillosis (IPA) is difficult [44]. Similarly, probable diagnosis of IPA can be itself underestimated because of the absence of the immunosuppressed status (in almost 65% of patients) and the lack of typical radiographic findings (in almost 95% of patients) [45,46]. Some experts consider as probable IAA diagnosis all cases with *Aspergillus* spp. isolation in the setting of severe influenza with multifocal lung infiltrates, until proven otherwise [39,47,48]. The prior use of antibiotics or steroids may increase the suspicion [48]. Blot *et al.* [47] do not consider Galactomannan antigen (GMA) detection because of poor accuracy and the risk of overtreating colonization. Moreover, a multicenter study in ICU patients with influenza, GMA detection in BAL and in serum showed a sensitivity of 94 and 67%, respectively [39].

EXTRAPULMONARY COMPLICATIONS

Influenza infections can rarely be complicated by a variety of nonpulmonary manifestations [49▪] (Table 4). Influenza infection can affect renal function through a number of complications including AKI, minimal change disease, rhabdomyolysis, and acute tubulointerstitial nephritis [49▪]. Data focusing on the pandemic period, only the presence of stage III of AKI has proven to be an independent risk factor for mortality [50]. Virus-associated muscular injury can manifest as myalgias or, less commonly, as rhabdomyolysis. Among critical patients with influenza, creatine kinase levels higher than 500 UI/L represent a severity index associated with greater respiratory and renal impairment [18].

Table 4. Extrapulmonary complication of influenza

Cardiac	Myocardial infarction
	Myocarditis and cardiomyopathy
	Congestive heart failure
	Arrhythmia
	Pericardial effusion
	Tamponade
	Myopericarditis
Neurologic	Encephalopathy/encephalitis
	Meningitis
	Seizure
	Stroke
	Transverse myelitis
	Guillains–Barre syndrome
Renal	Acute kidney injury
	Acute tubular necrosis, glomerulonephritis,
	Hemolytic uremic syndrome, myoglobinuria,
	rhabdomyolysis
Musculoskeletar	Myopathy, rhabdomyolysis
other	Hepatic, hematological, ocular, and endocrine involvement

The WHO surveillance case definition for influenza-like illness and severe acute respiratory infection.
Adapted from [49▪].

Influenza infection can exacerbate congestive heart failure and coronary disease through a number of mechanisms, including fever, hypoxia, proinflammatory cytokine storm, and procoagulant effects [51,52]. Data show a six-fold higher risk of myocardial infarction during the first week after diagnosis of influenza infection among high-risk population [53]. Myocarditis represents one of the contributors to morbidity and mortality during influenza infection, even in previously healthy patients [54]. Viral myocarditis has been reported in approximately 0.4–13% of cases. However, autopsy data found signs of inflammation and myocyte necrosis in 30–50% of fatal influenza cases, despite the absence of clinical cardiac involvement [49▪,55▪]. In the 2009 H1N1 pandemic, 58 cases of viral myocarditis were reported worldwide and 15 cases in Japan, with a mortality rate of about 30% [54]. A recent review found 44 cases of myocarditis following influenza in adult patients from 1959 to 2016, with 70% of cases in H1N1 pandemic periods [49▪]. Starting in 2017, a reversal in trend has been noted with an increase in severe cardiac damage related to influenza B [56▪]. Depending on the timing of presentation and the extent of myocardial involvement, presentation can range asymptomatic to acute heart failure with changes in cardiac enzymes and instrumental findings [54]. Around 90% of symptoms present between days 4 and 7

following the viral infection. Occasionally, cardiogenic shock and sudden cardiac death are the presenting symptoms in severe cases [55▪,57,58]. Elevation of cardiac troponin I and T levels is rarely described in viral myocarditis, compared to slightly higher but no specific increase of creatinine kinase myocardial band and serum myosin light chain I [49▪]. Among asymptomatic patients, nonspecific ST segment and T wave abnormalities and conduction disturbances resolve promptly within a week without changes in cardiac markers or echocardiography [59]. Moreover, QRS prolongation and reduction of ventricular function seems to be predictive signs of fulminant myocarditis [60]. At the same time, atrioventricular conduction block and ventricular fibrillation are the prevalent fatal arrhythmias associated with fulminant cases [54]. Echocardiogram may show ventricular wall thickening, reduced cardiac chamber size, and wall motion abnormalities, resulting in a significant reduction of ejection fraction for approximately 70% of cases [49▪]. In suspicion of viral myocarditis, coronary angiography can rule out coronary disease whereas MRI can distinguish myocarditis from myocardial infarction, showing altered enhancement in nonvascular territories [57,61]. When carried out, myocardial biopsy is not only useful for the diagnostic confirmation, but may also give information about prognosis, with a significantly better prognosis in case of lymphocytic cells compared to giant cell infiltrates [62]. Congestive heart failure is the most common complication and it has been described in more than 80% of cases, half of whom require advanced pharmacological and mechanical cardiac support therapies [49▪]. Both acute and chronic viral myocarditis can result in the development of a dilated cardiomyopathy as late sequelae [63].

Influenza-associated encephalopathy/encephalitis (IAE) is a complication that occurs during the first week of influenza infection, increasing morbidity and mortality [49▪,64]. The incidence has been estimated in up to 4% of hospitalized adults with a mortality of about 20%, affecting especially children [65–67]. Among adults, the large majority of IAE are described among immunocompetent patients without underlying neurological diseases [65,68]. The diagnosis of IAE is difficult to confirm because neurological symptoms usually can be coexistent during severe infections and influenza virus is rarely detected in cerebrospinal fluid (CSF). Confusion/sensory disturbance and seizures are the most prevalent neurological symptoms at admission, together with fever and inflammatory pattern on blood analysis [49▪,64,69]. Elevated white blood cell count and/or proteins in CSF are observed in almost half of patients [70]. Influenza virus RNA on CSF is positive in approximately 20% of cases, with a poor predictive negative value of test [49▪,65]. Nevertheless, all postmortem biopsies have yielded viral RNA isolated with perivascular lymphocytic infiltrates [64]. The EEG is not useful for the diagnosis, showing a nonspecific global slowing activity. CT scan showed findings in 50% of cases mostly described hypodense lesions in cortex and diencephalon [64]. In contrast, MRI was abnormal in all reviewed cases, involving signal abnormalities in grey and white matter, or brainstem [49▪,64]. According to neuroimaging, a broad spectrum of acute encephalopathy syndromes was identified, primarily described in the pediatric population [71]. These entities are the result of viral and cytokine storm damage, with different brain areas involved and neurological manifestations [72]. Conversely, immune mechanisms are likely operative in transverse myelitis and Guillane–Barré syndrome, with later time of onset [49▪]. According to pathogenesis, all patients with IAE received antiviral treatment and steroid therapy was added in the majority of them [70]. Moreover, consensus data on specific therapy is lacking and CNS penetration of oseltamivir is reportedly low in healthy patients [73].

CONCLUSION

Influenza infection remains a life-treating disease among ICU patients, being a major cause of ARF during the epidemic seasons. Early antiviral therapy and vaccination are the most effective ways of preventing deaths. Among ICU patient, primary pneumonia is the most common cause of death, indeed.

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Conflicts of interest

J.R. has participated as consultant for ROCHE and WHO. C.S. and P.P. declare no conflicts of interest.

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