

NARRATIVE REVIEW



Severe flu management: a point of view

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Abstract

Annual flu seasons are typically characterized by changes in types and subtypes of influenza, with variations in terms of severity. Despite remarkable improvements in the prevention and management of patients with suspected or laboratory-confirmed diagnosis of influenza, annual seasonal influenza continues to be associated with a high morbidity and mortality. Admission to the intensive care unit is required for patients with severe forms of seasonal influenza infection, with primary pneumonia being present in most of the cases. This review summarizes the most recent knowledge on the diagnosis and treatment strategies in critically ill patients with influenza, focused on diagnostic testing methods, antiviral therapy, use of corticosteroids, antibacterial and antifungal therapy, and supportive measures. The review focuses on diagnostic testing methods, antiviral therapy, use of corticosteroids, antibacterial and antifungal therapy, supportive measures and relevant existing evidence, in order to provide the non-expert clinician a useful overview. An enhanced understanding of current diagnostic and treatment aspects of influenza infection can contribute to improve outcomes and reduce mortality among ICU patients with influenza.

Keywords: Influenza, ICU, Antivirals, Corticosteroids, Mortality, Pneumonia

Introduction

Annual seasonal influenza varies in terms of severity, but carries very high morbidity and mortality. Patients with severe forms need to be admitted to the intensive care unit (ICU) and managed in this setting. The ICU experience since the 2009 pandemic has been essential in broadening our knowledge regarding diagnosis, treatment, and supportive management strategies for patients with severe influenza. Despite remarkable improvements in the prevention and management of influenza infection, cases of severe illness continue to be associated with complications, poor clinical outcomes, and substantial annual mortality [1]. This point of view article summarizes update knowledge on three key aspects related to the care of critically ill patients with influenza, that is, (a)

diagnostic testing methods; (b) treatment of severe influenza including antiviral therapy, use of corticosteroids, antibacterial and antifungal therapy; and (c) supportive measures. Experts were selected on the basis of their contrasted experience in the field of severe influenza, and included one pulmonologist, one specialist in infectious diseases, and two intensivists. Each of the section was assigned to one of the authors, but the final document was reviewed by the four authors. An extensive search of the literature was performed by the authors using MEDLINE/PubMed and Cochrane library databases, from 2009 to October 2019, aimed to retrieve relevant studies on diagnosis and treatment of influenza in ICU patients especially randomized controlled clinical trials (RTC), systematic reviews, meta-analyses, and expert consensus articles. In addition, opinions and statements here presented are supported by official guidelines of different international organizations and scientific societies, such as Public Health England (PHE) [2], the American Thoracic Society and Infectious Diseases Society of North America (ATS/IDSA) [3, 4], and the European Centre for Disease Prevention and Control (ECDC) [5].

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Diagnosis of influenza in critically ill patients

Evidence-based clinical guidelines recommend influenza testing in all hospitalized and critically ill patients with acute respiratory illness, including pneumonia (with or without fever) and acute worsening of chronic cardiopulmonary diseases, during periods of influenza activity [2–6]. At other time periods, testing is recommended in hospitalized patients with epidemiologic links (e.g., household/institutional contacts, travel history); however, since inter-seasonal outbreaks and sporadic infections also occur, testing in all critically ill patients with acute respiratory illness is advisable in clinical practice. Testing should be considered regardless of time from illness onset, time from hospital admission (i.e., nosocomial infections), host immune status, and vaccination history, because studies have shown that substantial proportions of hospitalized influenza patients (10–40%) are seasonal vaccine recipients [6–8]. Clinicians should be aware that testing should be performed as early as possible, as timing may have an impact both on test sensitivity (the viral load decreases over time, though prolonged shedding is expected in critically ill patients) and on clinical decision-making, including continuation/discontinuation of antiviral treatment, indication of additional testing and imaging studies, infection control measures, and clinical outcomes [9, 10]. Delayed diagnosis has been associated with higher risks of respiratory and renal failure as well as increased mortality [11].

The virological methods used to diagnose influenza infection have been reviewed in detail elsewhere [9]. Briefly and from a practical perspective, molecular (polymerase chain reaction, PCR) assays are regarded as the gold-standard for diagnosis; antigen-based assays are limited by their low sensitivity (40–70%, meaning that a negative test result does not rule out diagnosis; specificity 90–95%) [10, 12], and culture and serology are too slow or are retrospective, thus unhelpful in guiding clinical care (though useful in resistance testing and surveillance). Recently, the US Food and Drug Administration (FDA) demoted rapid influenza virus antigen detection test systems from class I to class II, owing to their poor diagnostic performance [13, 14]. The newer digital Immunoassays show improved sensitivity, though they remain less sensitive than molecular tests [12, 14]. Depending on the type of assay, PCR can detect all influenza A subtypes and B lineages with primers that target the conserved regions (e.g., M, NS), or individual HA subtypes using specific primers (e.g., H1, H3, H5, H7). Subtyping information may have implications for treatment (e.g., prepandemic H1N1 is oseltamivir-resistant) and may identify possible novel or avian strains (e.g., H1N1pdm09 and H7N9 were initially “untypeable” using existing primers) [9]. Since clinical manifestations of

Take-home message

The morbidity and mortality of patients with severe influenza is very high. A rapid viral and co-infection diagnosis, early oseltamivir treatment and adequate treatment of bacterial or fungal co-infections, avoiding corticosteroids that increase mortality, and optimal ICU supportive management, including ECMO if necessary, are the pillars for better outcomes in this critically ill population.

influenza are indistinguishable from infections cause by other respiratory pathogens, multiplex PCR platforms that detect a range of common viruses [e.g., influenza and subtypes, respiratory syncytial virus (RSV), parainfluenza virus, rhinovirus] and ‘atypical pathogens’ (e.g., mycoplasma, chlamydia, legionella) are increasingly being used in the clinical setting to guide management and infection control [9, 14]. The ‘turn-around-time’ of these assays varies depending on logistics and workflow [15].

More recently, molecular-based ‘point-of-care’ tests have become available for detecting influenza (and other viruses) at the bedside, offering a degree of accuracy comparable to conventional laboratory PCR assays. Several of these tests have already received the Food and Drug Administration Clinical Laboratory Improvement Amendments (CLIA) waiver for influenza virus detection [14, 16].

Growing evidence indicates that prompt diagnosis of a viral respiratory infection may enhance clinical decision-making and improve patient outcomes, allowing reductions in hospital admissions, triage time in the emergency department, duration of isolation, total length of stay, and use of ancillary laboratory tests, imaging studies and antimicrobials [15, 17–19]. A randomized controlled trial reported fewer in-hospital antibiotic prescriptions or earlier termination with rapid virological diagnosis [20]. However, the clinical impact and cost-effectiveness of these methods deserve further evaluation [18, 21]. Even using PCR, negative results may occur with nasopharyngeal samples in the case of influenza pneumonia due to differential viral kinetic changes along the respiratory tract ($\approx 10\%$) [6, 9, 10, 22]. In mechanically ventilated patients, lower respiratory tract samples (e.g., endotracheal aspirates or bronchoscopy specimens) should be collected, since the viral load is typically higher and shedding more prolonged than in the upper airways [6, 22, 23]. In patients who fail to respond or worsen with antiviral treatment especially individuals who have been exposed to antivirals or who are immunocompromised, resistance should be suspected [24]. In these cases, both phenotypic and genotypic resistance assays may be necessary (using baseline and subsequent samples), and consultation with an expert is advisable.

Phenotypic assays are evolving, and rapid tests for direct application to clinical samples are in development (e.g., iART, indicating oseltamivir ‘resistant’/‘non-resistant’; droplet digital PCR for target mutation) [24]. Genotypic assays provide a more accessible means for detection of resistance caused by mutations known to confer reduced susceptibility. The rapid result of a direct PCR assay on a targeted mutation, such as A(H1N1), H275Y; A(H3N2), R292K, E119V; A(H7N9), R294K, can be useful for guiding clinical management [24]. Next-generation sequencing allows simultaneous detection of quasi-species harboring resistance mutations even at low frequencies (1%), providing insights into intra-host viral genetic diversity and evolution including the emergence of variants with increased virulence (e.g., D222G, typically found in the lower respiratory tract of critically ill patients) [25–27].

The evidence in support of the use of biomarkers is limited. High C-reactive protein (CRP) levels have been reported in critically ill influenza patients with H1N1 infections, including those with bacterial coinfections, but its discriminatory value is doubtful [28, 29]. Low serum procalcitonin (PCT) levels may be helpful in ruling out bacterial coinfection and may allow earlier antibiotic discontinuation [30–34]. In critically ill patients, higher PCT stopping thresholds may be more appropriate (0.5 ng/mL) [35]. Recent research on host response signatures (e.g., transcriptomic profiling) to predict influenza disease progression or to assist differentiation between viral, bacterial, or viral–bacterial coinfections have shown promising results [9, 36–40]. The role

of immune testing including blood transcriptomic studies [41], while still in its infancy, will be probably relevant for the critical care physician in the forthcoming years. Elucidating the complex interactions of interferons, inflammatory cytokines, neutrophils, and complement/coagulation pathways in severe influenza could inform novel approaches for diagnosis and therapy [42].

A summary of diagnostic tests and their application in clinical practice is shown in Table 1.

Treatment of severe influenza

The treatment of severe influenza is vital to reduce mortality and morbidity. It can be divided into three parts: (a) antiviral treatment, (b) corticosteroid treatment and, (c) treatment of coinfection.

Antiviral treatment

The cornerstone of antiviral treatment in severe influenza is prompt initiation. The approved antivirals are neuraminidase inhibitors (NAI) and adamantanes. NAI include oseltamivir, zanamivir, and peramivir. These antivirals have activity against Influenza A, and B. Adamantanes (amantadine and rimantadine) are only active against Influenza A, but all currently circulating strains are resistant to these agents.

In meta-analyses in adult and pediatric outpatients, the administration of early oseltamivir reduced the duration of symptoms and influenza complications [1]. Unfortunately no RCTs have been carried out in hospitalized patients, but several observational studies confirm the benefit of early oseltamivir administration. The most

Table 1 Summary of diagnostic and testing methods for influenza infections

Diagnosis	
PCR	High sensitivity and specificity (‘gold-standard’) and rapid results; available singleplex assays detect influenza virus type (A, B) or subtypes (e.g., H1, H3, H5, H7); does not indicate infectiousness
Multiplex PCR	Available assays allow simultaneous detection of a panel of viruses (e.g., influenza subtypes, RSV, rhinovirus) and bacteria (e.g., mycoplasma, chlamydia, legionella) causing ARI
‘Point-of-care’ molecular tests	Rapid results at site of care; most available assays detect influenza A and B, and/or RSV
RIDT (& antigen-based assays)	Low sensitivity (40–70%); a negative result cannot rule out infection; demoted by FDA to class II device
Resistance testing	
Genotypic	Direct detection of known resistance mutations (e.g., H275Y, R292K) using specific PCR primers; results may assist clinical management
Phenotypic	Determination of antiviral’s IC_{50} in virus isolates (culture-based); identification of unknown resistance mutations
NGS	Allow detection of major and minor populations of virus variants, even at low frequencies (1%)
Surveillance and research	
Culture	Virus strain identification, virus titre quantification, infectiousness, phenotypic resistance assay; low sensitivity; slow results
Serology	Indicates infection and exposure (with/without virus detection); retrospective
Transcriptomic profiling	Host gene expression profiling may allow differentiation of influenza from other bacterial or viral causes of ARI

PCR polymerase chain reaction assay, RIDT antigen-based rapid influenza detection test, ARI acute respiratory infection, IC_{50} drug concentration required to inhibit viral neuraminidase

complete observational study is probably a pooled individual observational study [43] from 38 countries that showed a 38% reduction in mortality in the critically ill population aged over 16 years, and a 69% reduction in patients who received early treatment (>48 h). Comparing NAI treatment at any time versus no treatment, the reduction in mortality was 28%. In a phase 2 RCT, the combination of oseltamivir with adamantanes and ribavirin did not show any benefit over monotherapy with oseltamivir [44].

The timing of antiviral initiation is very important. Overall, antivirals obtain a clinical benefit if they are administered within 2 days of symptom onset; a large meta-analysis reported a 35% reduction in mortality risk when patients received oseltamivir within this time [43]. This study, however, was based on the administration within the first few days of symptoms (average of 2 days) yet it takes on average 5 days before a patient is admitted to the ICU [43]. Viral shedding has usually dropped dramatically and the deterioration is more likely related to host immune function rather than direct viral damage. NAI administration may be delayed when these patients arrive at the emergency department, and it is natural to recommend empirical initiation of NAI during the influenza season especially in patients with more severe disease.

The preferred NAI is oseltamivir, as no data are available regarding zanamivir in critically ill patients. In a 2017 RCT in hospitalized patients with influenza, intravenous zanamivir did not show superiority over oral oseltamivir [45]. Enteral absorption of oseltamivir is adequate and plasma levels are satisfactory in critically ill patients [46]. In patients with renal replacement therapy or extracorporeal membrane oxygenation (ECMO) [47], plasma levels are adequate using the enteral route, but doses need to be adjusted in patients with renal impairment. For patients with mild or moderate hepatic impairment (Child–Pugh score ≤ 9) no dose adjustment is recommended. It has been shown that in patients with ECMO, enteral oseltamivir reaches comparable serum levels than in non-critically ill patients. There is no evidence to increase doses of oseltamivir for a better efficacy in critically ill patients or in obese patients.

The duration of antiviral treatment in critically ill patients is controversial. A period of at least 5 days, and mostly 10 days is recommended in patients with severe pneumonia, and further treatment may be considered with persistent symptoms and virus detection, especially in the immunosuppressed [48, 49]. Antiviral resistance should be suspected when there is evidence of viral rebound and clinical non-remission [4].

On occasion, enteral treatment is not possible in critically ill patients, and an alternative is intravenous

peramivir. Studies of oseltamivir plus peramivir have not found any clinical difference between the use of peramivir (either alone or in combination) and oseltamivir administered by the enteral route [22, 50].

Baloxavir is a recently approved antiviral, but studies of its efficacy have only been performed in the outpatient setting. The role of this antiviral alone or in combination with oseltamivir in hospitalized patients is currently under investigation. Baloxavir has been approved by the FDA [51]. However, little is known at present regarding its resistances [52] and research into this issue is ongoing (trial identifier NCT03684044).

A recent phase IIb trial [53] of 5 days of treatment with pimodivir (a new class of antiviral, a polymerase inhibitor) compared doses of 300 mg, 600 mg, and 600 mg of pimodivir plus oseltamivir. Pimodivir-treated patients had a significantly lower RNA viral burden over time. Polymerase inhibitors appear to be promising for the treatment of patients with severe influenza infection. Two additional studies (trial identifiers NCT02532283 and NCT03376321) are currently underway. Again, resistance issues are not well known and are currently under investigation.

Dosing recommendations and schedule of administration of antivirals for adults are as follows: 75 mg twice daily orally for oseltamivir (including pregnancy); 10 mg (two 5 mg inhalations) twice daily for zanamivir; 600 mg intravenous infusion once given over 15–30 min for peramivir; and 40 mg single dose orally of baloxavir in patients of 40–80 kg of body weight and 80 mg in patients of >80 kg. Zanamivir, however, is not recommended in critically ill patients due to the lack of data in hospitalized patients and the risk of bronchospasm.

In summary, in critically ill patients with influenza, early enteral oseltamivir for at least 5 days is the mainstay of antiviral treatment. Treatment duration should be extended if viral tests remain positive. Resistance to oseltamivir should be considered in the case of prolonged persistence. Intravenous peramivir is the alternative when the enteral route cannot be used. Studies of new antivirals in hospitalized patients are currently ongoing.

Corticosteroid treatment

Concomitant corticosteroids have been administered in severe influenza to reduce the host immune response expressed by the hyperproduction of inflammatory cytokines. In fact, a Spanish ICU multicentre study revealed that up to one-third of patients with severe influenza had received concomitant corticosteroids [54]. However, many observational studies and three meta-analyses have demonstrated that concomitant corticosteroids are associated with increased mortality in severe influenza [55]. Findings of the study of Moreno and

co-workers [54] of 1849 patients from 148 Spanish ICUs are very illustrative; after adjusting for confounders, mortality increased in patients who received corticosteroids in the first 24 h.

Another multicenter study of 2649 patients receiving concomitant steroids for viral pneumonitis reported similar results. In that study, patients who received corticosteroids had increased nosocomial infections [7]. The time to administration of corticosteroids seems to be relevant, and two studies suggest that early administration within 3 days of admission is associated with increased mortality [7, 55]. In specific populations such as patients with chronic obstructive pulmonary disease (COPD) and immunosuppressed patients, corticosteroids also increase mortality. The most compelling evidence comes from a recent systematic review and meta-analysis published in 2019, including 10 studies and 6548 patients; there, corticosteroids were associated with higher mortality, longer ICU stay and higher rates of secondary infections but not days on mechanical ventilation [55]. In patients with concomitant bacterial infection the usefulness of corticosteroids has not been demonstrated [as it has in non-influenza-severe community-acquired pneumonia (CAP)]. Finally, it is not known whether the administration of corticosteroids in acute respiratory distress syndrome (ARDS) after several days of antivirals and with a negative viral test is beneficial or harmful.

In summary, corticosteroids should not be administered in patients with severe influenza especially concomitantly with the administration of antivirals, since they increase mortality and have a negative effect on other important outcomes. However, in severe influenza patients with septic shock and vasopressor-resistant hypotension, the risk/benefit of added hydrocortisone has to be considered.

Treatment of coinfection

Coinfections are frequent in severe influenza [7]. In a multicenter study in Spain of 2901 ICU patients with severe influenza, 16.6% had a coinfection and this proportion rose from 11.4% in 2009 to 23.4% in 2015 [56]. The main individual risk factors were old age and immunosuppression (HIV and medications). Importantly, coinfection was associated with longer ICU stay, and higher 28 days and in-hospital mortality. The main microorganisms found were *Streptococcus pneumoniae*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, methicillin-sensitive plus methicillin-resistant *Staphylococcus aureus* and *Haemophilus*. Legionella and atypical agents were also detected. *Aspergillus* spp. was isolated in a few cases. In a more recent multicenter study of immunosuppressed patients [57], not including HIV, coinfection was not

associated with higher mortality than in non-immunosuppressed patients. In the propensity matching analysis, influenza was not associated with mortality in this immunosuppressed population. Coinfection in severe influenza increases mortality in non-immunosuppressed patients but not in their immunosuppressed peers. *Aspergillus* spp. may coinfect patients with influenza; in fact, in a recent study including seven influenza seasons in non-immunosuppressed patients, influenza pneumonia was a risk factor for invasive aspergillosis. Mortality in patients with aspergillosis was twofold higher than that recorded in patients without this condition [58].

The diagnosis of coinfection is crucial to be established as soon as possible to administer an adequate antibiotic/antifungal treatment. A diagnostic work-up including a panel of non-invasive and invasive (if possible) viral/bacterial and fungal microbiologic methods is mandatory [9]. However, in many cases the treatment is empirical until microbiological results are available. In addition, it is very risky to base the decision to give antibiotic treatment on inflammatory biomarkers such as CRP or PCT, since they may be elevated in severe influenza (this diagnostic aspect is reviewed more in depth in the previous section).

From the practical point of view, in patients with severe influenza our advice is to add antimicrobial agents, such as a combination of a third-generation cephalosporin (ceftriaxone) plus a macrolides. A more advanced generation cephalosporin such as ceftaroline may be more suitable, since it covers *S. pneumoniae*, *S. aureus*, and non-extended-spectrum β -lactamase (ESBL) *Enterobacteriaceae* [59]. In case of risk factors for *Pseudomonas* spp. (severe COPD, bronchiectasis, corticosteroids, prior antibiotic treatment, malnutrition), an antipseudomonal antibiotic is advisable in addition to a macrolide. The coverage of *Aspergillus* spp. depends on its variability and prevalence in particular geographical regions. Immunosuppressed patients and patients with COPD and bronchiectasis present a higher risk.

In summary, empirical antibacterial treatment is always mandatory and should sometimes include antipseudomonal agents and/or antifungals (voriconazole). There is no evidence about the beneficial effect of other immunomodulatory adjuvant treatments [60], such as macrolides, acetylsalicylic acid, statins, or non-steroidal anti-inflammatory drugs.

Supportive treatment including ECMO

The major determinant of mortality in patients developing septic shock is the development of multiorgan failure (MOF). A unique characteristic of influenza is that while patients in their final stages may develop MOF,

respiratory failure is the main feature, with severe and in many occasions refractory hypoxemia [61].

Non-invasive ventilation (NIV) has been considered an attractive way of providing ventilatory support due to the absence of ventilator-associated complications, particularly ventilator-associated pneumonia (VAP) and other ventilator-associated infections. Many studies have failed to demonstrate a beneficial effect of NIV in severe CAP with hypoxemia; the evidence of its value in influenza is slim but it is still widely used [62]. A recent clinical review stated that NIV has no role in severe respiratory failure and in ARDS related to severe pH1N1 infection, and that transmission to healthcare professionals due to aerosol generation is an additional concern [63]. To date, no RCTs have assessed the use of NIV in influenza; the evidence comes from observational studies. One of the largest conducted so far is a multicenter study involving almost 2000 patients which assessed the usefulness of NIV in patients with acute respiratory failure due to influenza admitted to 148 ICUs using a decision tree analysis [64]. The major findings of the study were: NIV failure was frequent in patients with influenza infection, since one in two patients who initially received NIV eventually failed; ICU mortality was significantly higher in subjects with NIV failure (38.4% versus 31.3%, $P=0.01$) than in those receiving invasive mechanical ventilation; and NIV failure was associated with increased ICU mortality [odds ratio (OR) 11.4, 95% confidence interval (CI) 6.5–20.1]. Interestingly, SOFA was helpful for decision-making and that extremely sick patients (SOFA ≥ 5) had a higher risk of NIV failure and are not good candidates for this treatment. Taking into account the current literature, NIV should not be used in patients with influenza infection. Experience with high-flow nasal cannula (HFNC) oxygen therapy in influenza is very limited, and no randomized trials have been published. Probably the recommendation of NIV applies to HFNO to avoid delays in starting invasive mechanical ventilation and is restricted to patients with adequate saturation monitoring in areas under critical care supervision and non-severe hypoxemia needing higher oxygen flow rates.

In the case of severe hypoxemia, invasive mechanical ventilation is the mainstay of supportive therapy in ICU worldwide [65]. Patients with influenza are commonly affected by the inherent virulence of the virus, and the major feature is the early development of ARDS characterized by lung injury and primary viral pneumonia. The first approach is to provide what is known as a protective lung strategy with low tidal volumes (6 mL/kg) to avoid volutrauma and atelectrauma during invasive mechanical ventilation which might further damage the lungs, causing ventilator-induced lung injury and the local production and release of cytokines (biotrauma) [66].

If conventional invasive mechanical ventilation is unable to provide adequate levels of blood oxygenation, there are some other strategies that can benefit the patient. The first is the optimization of the ventilatory settings to improve lung recruitment [67] using PEEP titration methods one of which is electrical impedance tomography [68]. Mechanical ventilation asynchronies occur often during invasive mechanical ventilation [69]. Once detected, however, a crucial question is how to improve patient–ventilator interaction. To provide better patient–ventilator synchrony, two straightforward approaches should be considered. The first is the optimization of the patient/ventilator adaptation by increasing sedation/analgesia with or without a neuromuscular non-depolarizing agent and with ventilator adjustment or change in ventilator mode [70]. Questions about the use of muscle paralysis were raised after the recent publication of the National Heart, Lung, and Blood Institute PETAL Clinical Trials Network which showed no benefit in mortality in moderate-to-severe ARDS patients treated with early and continuous cisatracurium infusion [71]. The second strategy is prone positioning, which is gaining popularity because of its positive results for survival, benefits in oxygenation and lung recruitment, and the fact that ICU teams have become more familiar with this procedure [72]. We encourage placement of the patient in the prone position as soon as possible if severe hypoxemia occurs (PaO₂/FiO₂ ratio is below 150 mm Hg), since this strategy can improve oxygenation through several mechanisms, such as better distribution of ventilation, improved V/Q matching, and right ventricle unloading.

In some circumstances, none of the above strategies are possible. One technique that is returning to influenza treatment after some years of neglect is ECMO. The recent introduction of technological improvements has increased the use of ECMO (e.g., its latest generation oxygenator that optimizes membrane characteristics in favor of optimal gas exchange, the heparin-coated circuit, and the reduced damage to pumps due to magnetic levitation, etc.). ECMO is life-saving in potentially reversible acute respiratory failure associated with severe influenza A (H1N1) pneumonia that is not responsive to conventional therapies and has been extensively used for severe influenza; however, it remains a very costly, high resourced-intensive therapy, with a mortality rate that remains high. It has been applied all over the world in patients with severe hypoxemia and influenza, but its use has been very heterogeneous. In 2013, a meta-analysis with a limited number of 266 patients receiving ECMO for a median of 10 days found that mortality (mean mortality of 28%) varied widely (8% to 65%) depending on baseline patient features [73]. More recently, in another

Table 2 Summary of antiviral, antibacterial, and supportive treatments for severe for influenza infections

Management	
Antivirals: neuraminidase Inhibitors (NAI)	Oseltamivir (first line). Five days of duration but up to 10 days in immunosuppressed patients. Confirm good enteral transit. Adjust dosages in renal and hepatic failures. Discard resistances in refractory response Zanamivir and, Peramivir (Parenteral formulation) Baloxavir (not tested in ICU patients) Pimodivir (under investigation)
Corticosteroids	Avoid as no benefit. Associated to higher mortality and secondary infections. Balance risk/benefit of Hydrocortisone in refractory septic shock
Antibacterial treatment	As in severe community-acquired pneumonia in all patients with severe <i>Influenza</i> pneumonia (third G cephalosporin to cover <i>S. pneumoniae</i> , <i>S. aureus</i> , and <i>H. influenzae</i> : ceftriaxone, cefotaxime, ceftazidime, ceftobiprole) plus a IV macrolide (to cover atypicals plus Legionella) Cefazolin and ceftobiprole cover better <i>S. aureus</i> than ceftriaxone and cefotaxime. MS and MR strains only covered by ceftazidime and ceftobiprole Add antipseudomonal antibiotic in case of risk factors for <i>Pseudomonas</i> spp. (severe COPD, bronchiectasis, corticosteroids, prior antibiotic treatment, malnutrition, prior isolation)
Antifungal treatment	Suspicion on <i>Aspergillus</i> : a-Depends on the variability and prevalence in particular geographical regions b-Immunosuppressed patients and patients with COPD and bronchiectasis present a higher risk
Supportive treatment	Avoid NIV if ARDS If refractory hypoxemia: a-Optimizing patient/ventilator adaptation (with or without a neuromuscular non-depolarizing agent) b-Prone positioning (PaO ₂ /FiO ₂ ratio ≤ 150 mmHg) c-Avoid positive fluid balance -ECMO in refractory hypoxemia to a, b, c

ARDS acute respiratory distress syndrome, CAP community-acquired pneumonia, G generation, COPD chronic obstructive pulmonary disease, ECMO extracorporeal membrane oxygenation, NIV non-invasive mechanical ventilation, MS meticilin sensitive, MR meticilin resistance

systematic review and meta-analysis of 13 studies with a total of 494 patients receiving ECMO for severe influenza infection with respiratory failure, overall mortality (37.1%) was much higher than years before, and duration of pre-ECMO mechanical ventilation (in days) was the only statistically significant moderator of mortality identified [74]. Therefore, our recommendation would be that ECMO seems to be a feasible rescue therapy, which needs to be started soon after detecting refractory hypoxemia that does not respond to conventional therapies such as prone positioning. Accurate patient selection at baseline seems to be the most important factor for starting ECMO.

A summary of antiviral, antibacterial and supportive treatments for severe influenza infections is shown in Table 2.

Isolation and droplet precautions

In addition to standard precautions, patients with suspected or confirmed influenza should be isolated using droplet precautions [75, 76]. Although airborne transmission is not well established, the use of fit-tested particulate respirators (e.g., N95 masks) are recommended for aerosol-generating medical procedures (AGMPs) [75, 76]. Aerosol-generating procedures include endotracheal intubation, bronchoscopy, sputum induction, cardiopulmonary resuscitation, and open suctioning of airways [75].

Patients should be cared for in single rooms whenever possible [75–78]. If necessary, cohorting may be appropriate following individual risk assessment [77]. Isolation precautions for immune competent hospitalized patients should be continued for 7 days after illness onset or until 24 h after the resolution of fever and respiratory symptoms, whichever is longer [75, 77, 78]. Immune suppressed patients may continue to shed virus for prolonged periods of time despite minimal symptoms, often leading to continued infection control measures [75, 78]. Repeat sampling for influenza virus may be necessary in these patients to demonstrate viral clearance prior to discontinuation of isolation [78]; however, local infection prevention and control policies should be followed [77]. In addition, fit-tested N95 masks and airborne precautions for aerosol-generating procedures should be taken. General guidance is until symptoms resolve and longer if immunosuppressed.

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Compliance with ethical standards

Conflict of interest

AT is member of the advisory Board of Jansen for pimevidir. NL has previously received honoraria for consultancy work, speaking in educational programs, and/or travel support from: Shionogi Inc., Janssen Inc., Sanofi Pasteur Ltd., F. Hoffmann-La Roche Ltd., Genentech Inc., CIDARA Therapeutics Inc., all outside the submitted work. IL has no conflict of interest to declare. WS has no conflict of interest to declare.

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