Journal of Intensive Medicine 4 (2024) 160–174

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Review

Latest developments in early diagnosis and specific treatment of severe influenza infection

Francisco Valenzuela-Sánchez [1,2,3,*], Blanca Valenzuela-Méndez [4], Juan Francisco Rodríguez-Gutiérrez [2], Ángel Estella [1,5,6,*]

[1] Intensive Care Unit, University Hospital of Jerez, Ronda de Circunvalación s/n, Jerez de la Frontera, Spain
[2] Haematology Department, University Hospital of Jerez, Ronda de Circunvalación s/n, Jerez de la Frontera, Spain
[3] Centro de Investigación Biomédica en Red, Enfermedades respiratorias, CIBERES, Instituto de Salud Carlos III, Av. de Monforte de Lemos, Madrid, Spain
[4] Department of Oncological Surgery, Institut du Cancer de Montpellier (ICM), Parc Euromédecine, 208 Av. des Apothicaires,Montpellier, France
[5] Department of Medicine, Faculty of Medicine, University of Cádiz, Calle Doctor Marañón, Cádiz, Spain
[6] Instituto de Investigación e Innovación Biomédica de Cádiz (INIBiCA), Avenida Ana de Viya 21, Cádiz, Spain

ARTICLE INFO

Managing Editor: Jingling Bao/ Zhiyu Wang

Keywords:
Influenza
Pandemic
Respiratory failure
Acute respiratory distress syndrome
Intensive care unit admission

ABSTRACT

Influenza pandemics are unpredictable recurrent events with global health, economic, and social consequences. The objective of this review is to provide an update on the latest developments in early diagnosis and specific treatment of the disease and its complications, particularly with regard to respiratory organ failure. Despite advances in treatment, the rate of mortality in the intensive care unit remains approximately 30%. Therefore, early identification of potentially severe viral pneumonia is extremely important to optimize treatment in these patients. The pathogenesis of influenza virus infection depends on viral virulence and host response. Thus, in some patients, it is associated with an excessive systemic response mediated by an authentic cytokine storm. This process leads to severe primary pneumonia and acute respiratory distress syndrome. Initial prognostication in the emergency department based on comorbidities, vital signs, and biomarkers (e.g., procalcitonin, ferritin, human leukocyte antigen-DR, mid-regional proadrenomedullin, and lactate) is important. Identification of these biomarkers on admission may facilitate clinical decision-making to determine early admission to the hospital or the intensive care unit. These decisions are reached considering pathophysiological circumstances that are associated with a poor prognosis (e.g., bacterial co-infection, hyperinflammation, immune paralysis, severe endothelial damage, organ dysfunction, and septic shock). Moreover, early implementation is important to increase treatment efficacy. Based on a limited level of evidence, all current guidelines recommend using oseltamivir in this setting. The possibility of drug resistance should also be considered. Alternative options include other antiviral drugs and combination therapies with monoclonal antibodies. Importantly, it is not recommended to use corticosteroids in the initial treatment of these patients. Furthermore, the implementation of supportive measures for respiratory failure is essential. Current recommendations are limited, heterogeneous, and not regularly updated. Early intubation and mechanical ventilation is the basic treatment for patients with severe respiratory failure. Prone ventilation should be promptly performed in patients with acute respiratory distress syndrome, while early tracheostomy should be considered in case of planned prolonged mechanical ventilation. Clinical trials on antiviral treatment and respiratory support measures specifically for these patients, as well as specific recommendations for different at-risk populations, are necessary to improve outcomes.

Introduction

Annual influenza epidemics account for 3–5 million severe cases and 290,000–650,000 deaths worldwide;[1] In case of influenza pandemics, the consequences can be devastating. All known influenza pandemics have been caused by influenza A viruses (IAVs). The most virulent pandemic was the misnamed Spanish flu in 1918, caused by an H1N1 subtype. The virus infected approximately 30% of the population worldwide and resulted in>40 million deaths,[2] although recent studies indicate a death toll of approximately 100 million. Case fatality rates in subsequent pandemics were lower, estimated at

* Corresponding authors: Francisco Valenzuela-Sánchez and Ángel Estella, Intensive Care Unit, University Hospital of Jerez, Ronda de Circunvalación s/n, Jerez de la Frontera 11407, Spain.
E-mail addresses: pacovaes@yahoo.es (F. Valenzuela-Sánchez), litoestella@hotmail.com (Á. Estella).

https://doi.org/10.1016/j.jointm.2023.09.006
Received 10 May 2023; Received in revised form 19 September 2023; Accepted 26 September 2023
Available online 19 December 2023

0.03% of the global population during the 1957 Asian H2N2 influenza and the 1968 Hong Kong H3N2 influenza pandemics, and 0.01% during the first 12 months of the 2009 H1N1 pandemic.[3] The 1918 influenza pandemic was characterized by a higher mortality rate in young adults, as well as obese and pregnant women.[4] This phenomenon remains unexplained and was also observed during the 2009 pandemic. H1N1 influenza affects young individuals and patients with serious illnesses. Thus far, H1N1 influenza has been the leading cause of community-acquired viral pneumonia in adults. The rates of morbidity and mortality are high; the rate of hospitalization is approximately 10%, with 13%–45% of cases admitted to the intensive care unit (ICU). Despite advances in treatment, the mortality rate remains approximately 30%.[5] Therefore, early identification of potentially severe viral pneumonia is extremely important to optimize treatment in these patients. The objective of this review is to provide an update on the latest developments in early diagnosis and specific treatment of the disease and its complications, particularly with regard to respiratory organ failure. The most relevant studies were reviewed, and the information was structured in four sections (i.e., pathogenesis, biomarkers, diagnosis, and treatment).

Influenza Virus Pathogeny

Influenza virus pathogeny reflects the virus–host interaction and determines the severity of the disease. Influenza viruses belong to the *Orthomyxoviridae* family, characterized by a segmented, linear, negative-sense single-stranded RNA genome.[6] They are categorized into five genera (i.e., types A, B, C, Thogotovirus, and Isavirus). Influenza A and B viruses are responsible for seasonal epidemics.[7]

Virions have an aspherical shape and include a nucleocapsid containing eight single-stranded RNA fragments, a nucleoprotein, and the RNA polymerase complex.[8] The lipid envelope, derived from the cytoplasmic membrane of the infected cell, is located in the outermost part. Glycoproteins of viral origin, namely hemagglutinin and neuraminidase, are anchored to it as radial projections.[9] The neutralizing humoral immune response is directed toward those two antigenic determinants.[10] Hemagglutinin (the most abundant component) facilitates the binding of the virus to mucoprotein receptors on sialic acid-rich epithelial cells in the respiratory tract and fusion with the cell membrane.[11] The steps of influenza A replication are shared by other types of RNA viruses, with several viral proteins playing key roles in each of these processes: virus adsorption and endocytosis; synthesis of messenger RNA (mRNA) and replication of viral RNA; post-transcriptional processing of viral mRNA; translation and post-translational processing of virus proteins; and virus assembly and release from cells (Figure 1).[12]

The IAV exhibits a marked capacity to undergo variations in its antigens, particularly surface antigens, with major epidemiological implications. A (H1N1) and A (H3N2) are the subtypes currently circulating in humans. A (H1N1), also termed A (H1N1)pdm09 as it caused the 2009 pandemic, subsequently replaced the seasonal influenza A (H1N1) virus circulating until then. Type B viruses are not classified into subtypes; however, the currently circulating viruses can be divided into two lineages, namely B/Yamagata and B/Victoria.[7]

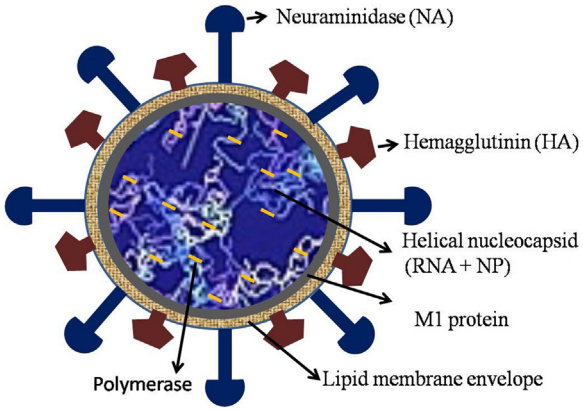

Figure 1. Schematic of the structure of the influenza A virion. NP: Nucleoprotein.

The H1N1pdm09 virus differed considerably from the H1N1 viruses circulating at that time. In typical epidemics, the highest mortality rates occur in individuals aged >65 years. Nevertheless, during the last epidemic, it was estimated that 80% of deaths occurred in individuals aged <65 years. These data confirm the presence of cross-reactive antibodies in individuals aged >60 years, as well as the lack of such antibodies in children and adults.[13]

The innate immune system is the first line of defense against infectious agents and is essential for the control of numerous infections. However, this system is not effective in eliminating the infectious agent in all cases and is unable to recognize certain germs. The cells of the innate immune system initiate and direct the adaptive response, aiming to neutralize the aggressor. In addition, a compensatory anti-inflammatory response and a process of tissue damage repair must be generated. Importantly, if this response becomes a systemic reaction, it may lead to catastrophic results. For example, sepsis is the uncontrolled inflammatory response induced by infection.[14,15]

The immune response generated following influenza infection is crucial for the control of infection. However, it can also determine the development of excess inflammation and disease.[16,17] Therefore, an aberrant immune response, conditioned by the basal state of the host or induced by the germ, is associated with an excessive response. This response facilitates the development of primary pneumonia, acute lung damage, bacterial superinfection, and systemic involvement (Figure 2).[18]

In most cases, the influenza virus produces a disease with mild symptomatology; nonetheless, severe complications can develop in certain susceptible populations (e.g., pregnant women, obese, immunocompromised), potentially resulting in death[19] (Table 1). The pathogenesis of influenza virus infection depends on viral virulence and host response.[20] It has been documented that immunocompromised patients with severe influenza pneumonia were at a higher risk of developing severe acute respiratory distress syndrome (ARDS) and at a three-fold higher risk of death in the ICU compared with non-immunocompromised individuals. Nevertheless, these differences were not explained by higher rates of co-infection or nosocomial pneumonia, suggesting that the influenza virus itself was responsible for a more severe form of pulmonary disease in immunocompromised patients.[21]

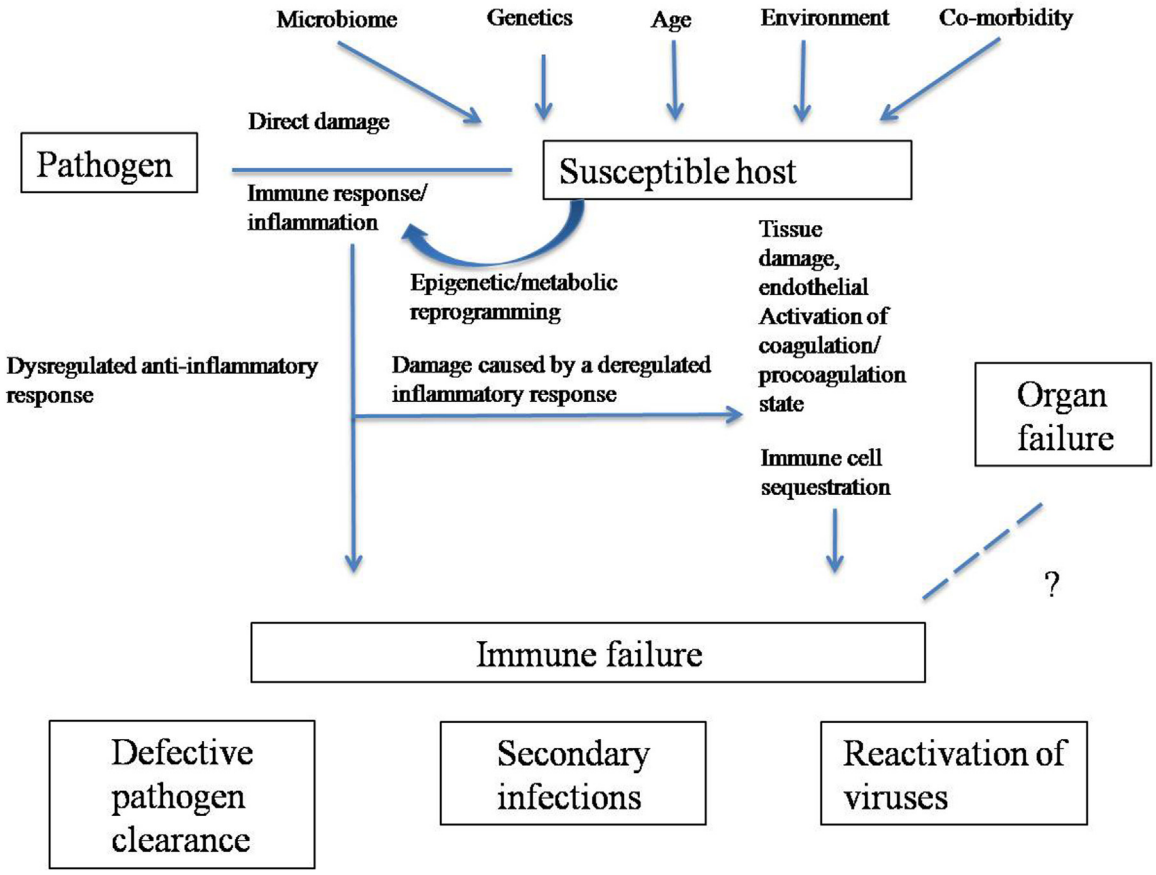

Figure 2. Key events in the immunopathology of influenza sepsis (adapted from Rubio et al.'s study[18] with permission from the authors).

Table 1
Immunological abnormalities described in normal, pregnant, and obese patients with pneumonia due to influenza.

Items	Normal patients	Pregnant patients	Obese patients
Cell populations	Increase in number of lymphocytes. Decreased NK% ($CD3^-/CD56^+$) cells are associated with increased mortality.	Increased number of cells at the expense of T $CD4^+$ cells.	Increase in absolute number/percentage of eosinophils and monocytes (which leads to a chronic inflammatory state). Decrease in the absolute number/percentage of lymphocytes and granulocytes.
CD4/CD8 ratio	Increased	Increased	Increased
Neutrophil and dendritic cells migration	Unaltered or increased	Unaltered or increased	Decreased
Th1/Th2 balance	Increased	Decreased	Increased
IL	Increased IL10 Increased IL 6 Increased IL 2	Increased IL10 Decreased IL 2	Decreased IL10 Increased IL 8 Increased IL 6, TNF Decreased IL 4 Increased IL 3 Decreased IL 2
TNF-α	Unaltered or decreased	Unaltered or increased	Increased
IFN-Υ	Decreased	Decreased	Decreased
Leptin	Unaltered	Increased	Increased
Adiponectin	Unaltered	Decreased	Decreased
Ferritin	Increased (levels >2000 ng/mL are associated with increased mortality)	Decreased	Increased

IFN-γ: Interferon-gamma; IL: Interleukin; NK: Natural killer; Th1: T helper 1; TNF: Tumor necrosis factor.

Older patients may have an unbalanced immune system due to aging. Thus far, few admissions of older patients to the ICU due to severe influenza infection have been reported.[22] This finding is attributed to several reasons, including higher rates of vaccination that prevent the development of more severe clinical forms of this infection. Importantly, age *per se* should not be an exclusion criterion for ICU admission. Nevertheless, it is well established that older age is associated with greater comorbidity and may influence clinical decisions regarding the administration of conservative treatment in this patient population. Although the management of influenza infections in the ICU for elderly patients is similar to that of other patients, careful

individualized optimization of treatment for meticulous fluid management is necessary based on differences in the hemodynamic resuscitation.

Severe pneumonia is the main pathology caused by influenza treated in the ICU. Patients with ARDS who develop cardiac complications due to influenza may also be admitted to the ICU. Influenza myocarditis is a rare and potentially underdiagnosed condition that can be fatal.[23] During epidemics, the presence of viral myocarditis must be considered in patients who present with cardiogenic shock. It has been revealed that right ventricular dysfunction is more common than left ventricular dysfunction in critically ill patients.[24] Early diagnosis and treatment of influenza myocarditis is crucial to prevent fatal complications. Other extrapulmonary complications are rare, and influenza-associated encephalitis is mostly observed in the pediatric population.[25] In adults, this rare complication occurs in a small proportion of patients,[26] and is frequently associated with metabolic disorders. Our review of the literature revealed that influenza-associated encephalitis is rarely reported in patients admitted to the ICU.

Biomarkers

Immune biomarkers in severe influenza pneumonia

An individual history of immunosuppression, treatment with immunosuppressive drugs, and the presence of hematological diseases or acquired immunodeficiency syndrome are not associated with a poor prognosis of severe pneumonia caused by influenza A (H1N1vIPN).[4,27] Our data support this notion; in our previous study,[28] the course of disease evolved favorably for 16 of 21 patients with a history of immunosuppression (e.g., acquired immunodeficiency syndrome, corticosteroid treatment, chemotherapy, or severe malnutrition). Notably, two patients with hematological malignancies (i.e., myeloma and leukemia) were considered immunocompromised.

In recent years, research enhanced our knowledge regarding the mechanisms underlying sepsis-related immune dysfunction. However, clinical trials testing immune intervention strategies in patients with sepsis have been unsuccessful. Venet et al.[29] proposed that patient stratification is the key to success in future studies, according to the characteristics of the infection, patient-specific parameters, and the immune status of patients. Therefore, patient stratification based on biomarkers may be a prerequisite in clinical trials evaluating immunomodulatory therapies in this setting. Thus far, the absolute lymphocyte count and decreased human leukocyte antigen-DR (HLA-DR) expression in monocytes appear to be the most robust markers for patient stratification in multicenter clinical trials.[30]

HLA-DR expression in monocytes plays an important role in the aberrant immune response, with decreased expression observed on admission in patients admitted to the ICU. Decreased expression of HLA-DR in circulating monocytes is a marker of immunoparalysis.[31,32] In influenza infection, this is of great relevance, as the T-cell response to hemagglutinin molecules is restricted by HLA-DR molecules. This may lead to an ineffective immune response, which is associated with a poor prognosis. Diao et al.[33] reported lymphopenia in both mild and severe cases of H7N9 infection. However, a marked reduction in HLA-DR expression in monocytes was negatively correlated with disease severity. We documented significantly lower numbers of lymphocytes, monocytes, and natural killer cells, as well as lower HDL-DR expression in monocytes among non-survivors. In addition, non-survivors showed a higher proportion of B cells and higher levels of immunoglobulin A (IgA) and IgM. These findings confirm a poor cell-mediated immune response and a sustained presence of the virus in the extracellular stage of the viral life cycle.[34] In this study, we identified four different immunological phenotypes, according to the levels of ferritin and HLA-DR (Figure 3), showing the importance of immunosuppression in prognosis and its relation to the inflammation status.

Immune dysfunction, expressed by decreased numbers of T and natural killer lymphocytes, as well as decreased numbers and dysfunction of monocytes (i.e., with lower HLA-DR expression), was associated with increased mortality among patients hospitalized with H1N1pdm09 influenza A pneumonia. A significant increase in mortality was also documented in the presence of hyperinflammation. Early monitoring of the immune response and subsequent stratification of patients may be helpful in designing personalized management strategies [35] with immunomodulatory therapies.

Biomarkers of co-infection/overinfection in severe influenza pneumonia

The prevalence of bacterial co-infection in patients with influenza is currently unknown. In a systematic review and meta-analysis highlighting the great heterogeneity of published studies, this prevalence was in the range of 2%–65%.[36]

The introduction of routine techniques, such as polymerase chain reaction (PCR), has broadened the etiological spectrum of respiratory infections. It has been shown that a significant proportion of cases present as viral co-infections, particularly during winter, and the types depend on the viruses circulating at that time. However, the clinical significance of mixed infections is unclear because, in many cases, viruses can be detected beyond the acute episode due to the high sensitivity of molecular tests.[37]

Secondary bacterial pneumonia, which occurs in both adult and severe pediatric patients (25%–50% of cases), is responsible for high rates of morbidity and mortality. The most frequent microorganisms causing secondary bacterial pneumonia are *Streptococcus pneumoniae* and *Staphylococcus aureus*.[38,39] The mechanisms by which the risk appears to be increased include cellular damage caused by the virus, secondary dysregulated immunity, or alteration of the secondary gut microbiota.[40]

According to the literature,[41] patients with influenza A who are admitted to the ICU or who expired show significantly higher C-reactive protein (CRP), procalcitonin (PCT), and ferritin levels on admission to the emergency department (ED). In our previous study,[42] we reported that PCT levels measured in the ED in adults with H1N1vIPN without bacterial co-infection were similar to those measured in patients not admitted to the ICU. Moreover, there were no significant differences in mortality between the groups. PCT is considered a sensitive marker for bacterial infections and is responsible for the difference noted between risk groups due to a higher rate of co-infection on admission in critically ill patients.[28] Notably, the levels of PCT were even higher in the influenza B group with an extremely high incidence of co-infection (57.4%). Measurement of PCT can help

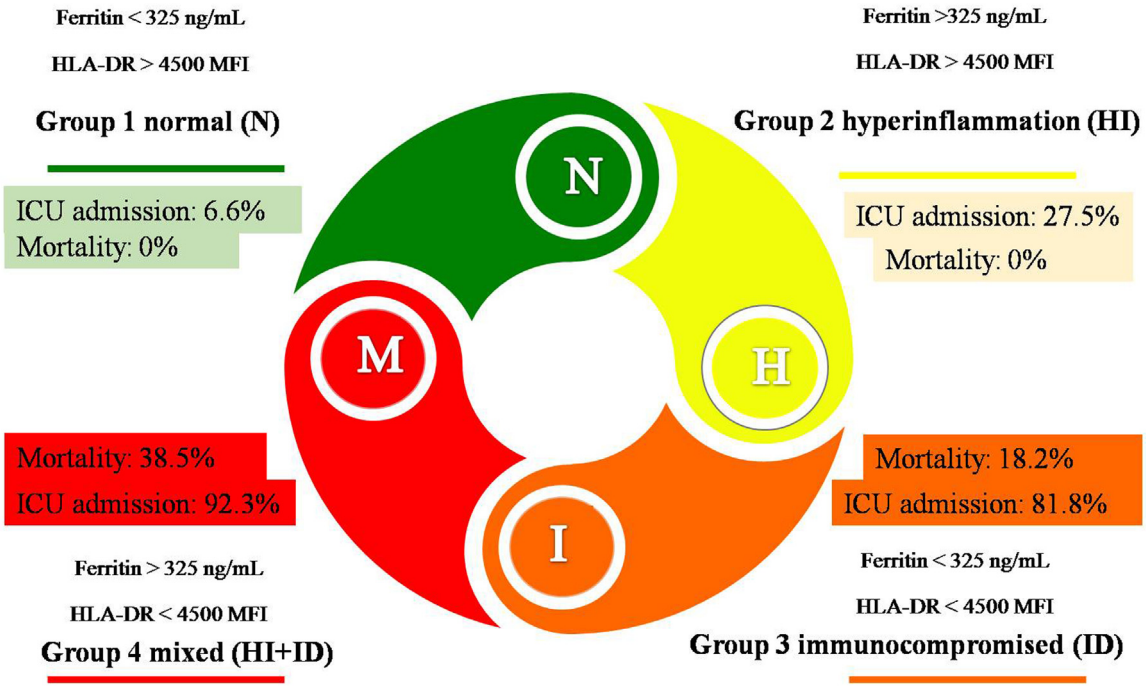

Figure 3. Immunophenotype groups in patients with influenza A H1N1pdm09. Diagram of the four immunophenotypes according to ferritin levels and HLA-DR expression. An increase in mortality is observed in groups with immunoparalysis (ID and HI + ID) (adapted from Valenzuela-Méndez et al.'s study[34] with permission from the authors).
HI: Hyperinflammation; HLA-DR: Human leukocyte antigen-DR; ICU: Intensive care unit; ID: Immunocompromised; MFI: Median fluorescence intensity.

discriminate between severe lower respiratory tract infections of bacterial origin and H1N1vI. In patients admitted to the ICU with H1N1vIPN, PCT is a sensitive marker with a good negative predictive value for detecting bacterial infections and is superior to CRP levels. Low PCT values, particularly when combined with low CRP levels, suggest the absence of bacterial infection, either alone or in combination with influenza.[43,44]

Biomarkers of organ failure in severe influenza pneumonia

The mid-regional proadrenomedullin (MR-proADM) is a biomarker of organ failure.[45] It was previously described that the levels of adrenomedullin in cardiovascular pathologies were markedly increased in patients with septic shock.[46]

Numerous studies have demonstrated the usefulness of MR-proADM levels in the diagnosis [47–49] and prognosis of patients with bacterial sepsis [50,51]; their high levels reinforce the usefulness of PCT in the early diagnosis of patients with sepsis when used in combination. MR-proADM levels are more prognostically useful in patients with lower clinical severity, and their clearance during the evolution of infection is related to good prognosis. Their effectiveness in other critical viral infections, such as coronavirus disease-2019 (COVID-19), has been widely reported; in addition, it has been shown that MR-proADM levels are particularly useful with regard to prognosis.[52–54]

We previously demonstrated [42] the prognostic value of MR-proADM and PCT levels measured in the ED in adults with H1N1vIPN without bacterial co-infection, showing significant difference in MR-proADM levels between the mortality groups. Subsequently, we reported more broadly that MR-proADM levels in patients admitted to the ED with influenza A pneumonia can predict the severity of illness, poor outcome, risk of ICU admission, need for mechanical ventilation (MV) and mortality. In addition, we have demonstrated the prognostic superiority of MR-proADM levels over other markers (e.g., CRP, PCT, and ferritin) and the Sequential Organ Failure Assessment Score (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) severity scoring systems.[28]

Diagnosis

Etiology

Pneumonia due to the influenza virus is defined as a lower respiratory tract infection characterized by clinical signs and symptoms of respiratory infection and radiological opacities observed on chest X-ray examination (consistent with pneumonia),[55] as well as a positive result in a diagnostic test using a respiratory specimen for influenza virus.

Prompt diagnosis of influenza offers multiple advantages in clinical decision-making, such as reductions in admission rates, length of stay in the ED, isolation time, cost for diagnostic tests, and unnecessary use of antibiotics.[56] Early testing is recommended for any pneumonic infiltrate or chronic obstructive pulmonary disease decompensation in patients with respiratory failure, particularly during influenza infection.[57] The diagnostic test used in such cases should be reverse transcription polymerase chain reaction (RT-PCR).

The diagnostic criteria are the presence of clinical symptoms with pulmonary infiltrate and a positive RT-PCR for influenza. Samples are obtained from pharyngeal secretions and bronchial aspirates or through bronchoscopic bronchoalveolar lavage. Other methods, such as antigen determination, have yielded false-negative results due to their low sensitiv-

ity (40%–70%).[57] Furthermore, culture and serology are time-consuming, expensive, and impractical methods. The tests are used to determine the subtypes of influenza, which is a very important aspect with therapeutic implications. In critically ill patients, the rate of intubation is high, and diagnostic assessment can be performed by bronchial aspiration or bronchoalveolar lavage. These methods are linked to cost-effectiveness owing to the increased viral load present in the lower respiratory tract.[58]

Prognosis

Regarding prognosis, the use of biomarkers on admission (e.g., PCT, ferritin, HLA-DR, and MR-proADM) may provide data regarding possible co-infection, hyperinflammation status, immune status, and endothelial disruption. Moreover, biomarkers can determine the degree of organ failure, thereby providing an early indication of the need for admission to the ward or ICU and avoiding a potentially dangerous hospital discharge.[28,34] A Quick Sequential Organ Failure Assessment Score (qSOFA) or SOFA ≥2 or lactate levels ≥2 mmol/L also indicate a significant degree of severity or shock, respectively [59] (Table 2).

Early admission to the ICU: protocol

The clinical criteria for ICU admission (severity criteria of the American Thoracic Society/Infectious Diseases Society of America) are as follows: major criteria (presence of 1 criterion) include the need for MV or the presence of septic shock; minor criteria (presence of ≥2 criteria) include systolic blood pressure (BP) <90 mmHg, respiratory rate >30 rpm, PaO_2/FiO_2 <250, multilobar infiltrates, confusion, urea levels >55 mg/dL, hypothermia, leukopenia, or thrombocytopenia.[55,60]

In numerous cases, these signs/symptoms are not manifested early; in addition, respiratory failure, which is life-threatening, occurs unexpectedly and requires emergency intubation. Rapid biomarker assessment is required to safely reach a decision regarding hospital or ICU admission that would ensure the provision of the necessary supportive care. In our previous study,[28] MR-proADM levels >1.2 nmol/L at hospital admission denoted severe respiratory failure requiring ICU admission, and a high proportion requiring MV. Values >1.2 nmol/L indicate poor prognosis in patients admitted to the ICU. This cut-off point detects mortality with a sensitivity of 100% and a maximum negative predictive value. Ferritin levels ≥625 ng/mL and PCT values ≥0.275 ng/mL were also effective in determining severity and mortality, with negative predictive values of 93.7% and 98.2%, respectively.[28] The determination of these biomarkers on admission can be decisive in determining early admission to the ICU. This approach considers pathophysiological circumstances that individually or in combination are associated with a poor prognosis: bacterial co-infection; hyperinflammation; immunoparalysis; severe endothelial damage; organ dysfunction; and septic shock (Table 2).

Influenza A infection can lead to mild symptoms that can be treated at home, require admission to a hospital ward, or even require invasive treatment and close specialized follow-up in the ICU. In the initial approach for appropriate decision-making, we propose using analgorithm shown in Figure 4.

Table 2
Rapid laboratory biomarkers (PCT, ferritin, HLA-DR, MR-proADM, and lactate) and clinical scores (SOFA and qSOFA).

Biomarkers	Cutting point	Pathogenic significance
PCT	>0.275 ng/mL	Co-infection/overinfection
Ferritin	>625 ng/mL	Hyperinflammation
HLA-DR	<4500 MFI	Immunoparalysis
MR-proADM	>1.2 nmol/L	Endothelial damage/organ dysfunction
Lactate	>2 mmol/L	Septic shock
SOFA/qSOFA	≥2	Organ dysfunction

HLA-DR: Human leukocyte antigen-DR; MFI: Median fluorescence intensity; MR-proADM: Mid-regional proadrenomedullin; PCT: Procalcitonin; qSOFA: Quick Sequential Organ Failure Assessment Score; SOFA: Sequential Organ Failure Assessment Score.

Treatment

The global inability to effectively manage emerging viral infections was demonstrated in the 1918 influenza pandemic, as well as in the subsequent viral epidemics, such as the 2009 influenza pandemic, the Ebola outbreak in Africa (2013–2016), and the COVID-2019 pandemic.[61] This inability to respond effectively has important social and economic consequences worldwide.[62] Therefore, the effectiveness of antiviral and supportive treatments must be evaluated on an individualized basis through appropriate studies. A high rate of drug resistance has been observed, which is associated with certain profiles of high-risk hosts and the peculiarities of lung lesions produced by each virus.[61]

Prevention and proactive vaccination planning for influenza could help to reduce the pressure in the ICU during epidemic periods. Vaccine effectiveness has been demonstrated (Centers for Disease Control and Prevention Influenza): Past Seasons Vaccine Effectiveness Estimates (available from:https://www.cdc.gov/flu/vaccines-work/past-seasons-estimates.html [last accessed on 2023 September 1]). During the 2009 influenza pandemic, an unprecedented number of patients with severe viral pneumonia developed ARDS in the ICU. It has been documented that vaccination is more effective in avoiding admission to the ICU rather than to a hospital ward:[63] vaccines have also shown effectiveness in preventing the development of the most severe clinical forms of the disease.

Several treatment options have been developed for the treatment of such infections (e.g., antivirals, monoclonal antibodies [mAb], corticosteroids, antibiotics, antifungals, and supportive measures) (Table 3).

Antivirals

Almost all current guidelines recommend the administration of antiviral drugs as early as possible, particularly in patients at risk of severe disease. Three classes of antiviral drugs (i.e., M2 blockers, neuraminidase inhibitors, and the polymerase acid inhibitor that blocks viral replication) have been approved in many countries for the management of influenza A infections. A new class of agents, termed cap-dependent endonuclease inhibitors, is currently under investigation.[64] The rapid evolution of the influenza virus, leading to reduced vaccine efficacy and the emergence of drug-resistant strains, is driving ongoing research into the development of new antiviral drugs. Currently, research is focused on several directions, including substances of synthetic, biological (bacterial), and plant origin.

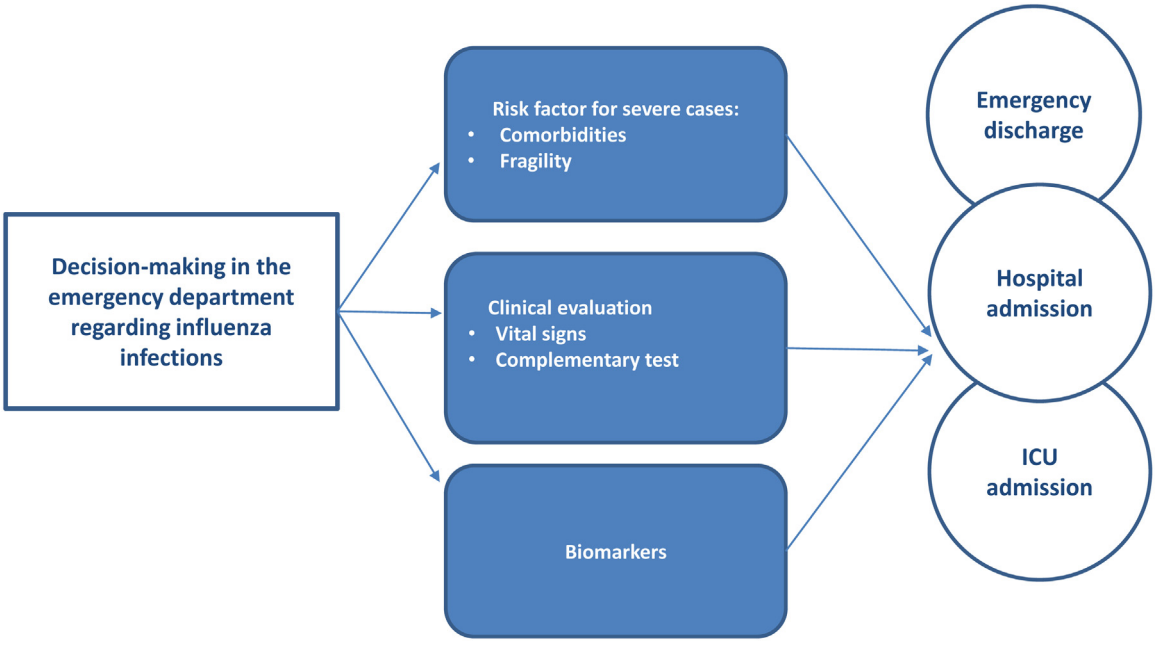

Figure 4. Algorithms for deciding the destination of patients with severe influenza in the Emergency department by assessing risk factors, clinical assessment with rapid laboratory markers (PCT, ferritin, HLA-DR, MR-proADM, and lactate), and clinical scores (SOFA and qSOFA).
HLA-DR: Human leukocyte antigen-DR; ICU: Intensive care unit; MR-proADM: Mid-regional proadrenomedullin; PCT: Procalcitonin; qSOFA: Quick Sequential Organ Failure Assessment Score; SOFA: Sequential Organ Failure Assessment Score.

Table 3
Summary of the intensive care management of severe influenza infection.

Intensive care management of severe influenza infection	Treatment	Indication	Dosage and administration	Adverse events	Caution
Antivirals	Oseltamivir (first line). (parenteral or resistance: zanamivir, peramivir)	Treatment and prophylaxis	75 mg/12 h orally 5–10 days (persistent symptoms or immunosuppression)	Headaches and digestive disorders	Drug resistance, enteral intolerance, renal insufficiency
Monoclonal antibodies	Currently in clinical research				
Corticosteroids	Hydrocortisone	Not recommended (risk/benefit in refractory septic shock or ARDS + negative RT-PCR)	200 mg/day	Higher mortality, longer ICU stays, and a higher rate of secondary infection	
Antibiotics	Against *Staphylococcus* and *Streptococcus* spp.: ceftaroline	Empirical antibiotic therapy pending bacteriological cultures	600 mg/12 h 5–7 days according to clinical course, bacteriological cultures, or PCT		
Antifungals	First line: isavuconazolor, voriconazol Second line: liposomal amphotericin B	Anticipated antifungal therapy if high suspicion of IAPA	Isavuconazol: 3 × 200 mg/day during the first 48 h Continue with 200 mg/day for 3 days Voriconazol: 2 × 6 mg/(kg·day) for 1 day Continue with 2 × 4 mg/(kg·day) for 2 days Liposomal amphotericin:3 mg/(kg·day)		Voriconazol requires therapeutic drug monitorization. Voriconazol is not recommended with renal insufficiency
Organ support therapy	■ Avoid NIV or HFNC in severe pneumonia with ARDS criteria. ■ Early elective intubation ■ Lung protective ventilation ■ Early prone ventilation in patients with ARDS criteria ■ Optimal sedation and relaxation ■ Early tracheostomy should be considered if prolonged ventilation expectation ■ ECMO if refractory hypoxemia ■ Advanced hemodynamic monitoring ■ Personalized hemodynamic resuscitation				

ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; HFNC: High-flow nasal cannula; IAPA: Influenza-associated pulmonary aspergillosis; ICU: Intensive care unit; NIV: Non-invasive mechanical ventilation; PCT: Procalcitonin; RT-PCR: Reverse transcription polymerase chain reaction.

Oseltamivir

Oseltamiviris available for treatment and prophylaxis against influenza A and B in capsules (30 mg, 45 mg, 75 mg) and powder (6 mg/mL) for oral suspension.[65] It is the most recommended and used agent despite limited evidence regarding its clinical usefulness in critically ill patients.[66] Specifically, there are no randomized controlled trials on its usefulness in this setting. A multicenter observational study showed a 38% reduction in mortality among patients in whom treatment was initiated within 48 h of symptom onset. Initiation of treatment at a later stage was linked to less benefit.[67] Furthermore, polytherapy did not offer advantages over monotherapy.[68] Due to its high cost and potential adverse reactions, it is not recommended to use oseltamivir if the causative strain is resistant to this agent.[69] Use of this drug is recommended in pregnant patients, particularly those who are asthmatic.[70]

Drug resistance should be suspected in patients who do not respond to antiviral treatment or exhibit a deterioration, especially those who have been exposed to antivirals or are immunocompromised.[71] Prompt (≤48 h) enteral administration is recommended, although the maxim “late is better than never” applies. The duration of treatment is set at 5 days and 10 days for moderate and severe cases of pneumonia, respectively. This period could be extended in case of persistent symptoms or immunosuppression, while considering the possibility of drug resistance.[72]

In critically ill patients, enteral absorption of oseltamivir is adequate and plasma levels are satisfactory. In patients receiving renal replacement therapy, administration via the enteral route results in adequate plasma levels; however, the dose needs to be adjusted depending on the rate of creatinine clearance. Dose adjustment is not recommended for patients with mild or moderate hepatic impairment (Child–Pugh score ≤9). In patients receiving extracorporeal membrane oxygenation (ECMO), enteral administration of oseltamivir results in comparable serum levels to those detected in non-critically ill patients. At present, there is no evidence indicating that an increase in the dose of oseltamivir improves its efficacy in critically ill or obese patients.[55]

Patients with highly suspected influenza infection should be treated with oseltamivir (75 mg orally, twice daily for 5–10 days) depending on the severity of symptoms and the clinical picture. Oseltamivir is well tolerated, with headaches and digestive disorders described as the most frequent side effects. Rapid initiation of treatment affects the prognosis of this disease.[64]

Zanamivir

Zanamivir was the first neuraminidase inhibitor approved and used for the treatment and prevention of influenza A and B infections.[73] The agent was initially prepared in the form of an off-white powder for inhalation. Currently, there are no data available on the usefulness of zanamivir in critically ill patients. In 2017, a randomized controlled trial involving hospitalized patients with influenza was carried out. The results showed that intravenous zanamivir was not superior to oral oseltamivir.[74]

The administration of zanamivir has been associated with bronchospasm crises. Gastrointestinal disturbances and liver dysfunction have also been reported. Use of this agent is contraindicated in patients with an allergy to milk protein and those with glucose/galactose malabsorption due to the lactose content of the excipient. It should be administered with caution to patients with asthma and chronic obstructive pulmonary disease, pregnant women, and the elderly.[64]

The recommended dose is 5 mg inhaled twice daily for 5 days within 48 h of symptom onset. For prophylaxis, zanamivir can be administered at a dose of 10 mg once daily for up to 36 h after contact with the patient for 10 days. Since 2019, a preparation for intravenous infusion has also become available for the treatment of patients with severe illness, sepsis, gastrointestinal intolerance, obstruction, or malabsorption. The recommended dose is 600 mg twice daily during the first 6 days following symptom onset for 5–10 days. In case of renal insufficiency, the dose should be adjusted depending on the rate of creatinine clearance.

Peramivir

Peramivir was initially approved in Japan and subsequently in the USA and Europe, where it is currently withdrawn for commercial reasons by the manufacturer.[75] This drug is administered through a single intravenous dose, thereby offering simplicity. It is currently used as an alternative option in patients who exhibit intolerance or resistance to oseltamivir.[76] Comparative studies have not shown an advantage after treatment either as monotherapy or in combination with oseltamivir administered enterally.[56] The recommended dose is 600 mg as a one-time intravenous infusion over 15–30 min within 48 h following symptom onset. The need for dose escalation in patients with severe disease is currently under investigation.[64]

This drug interacts with live attenuated vaccines. Thus, it is recommended to perform vaccination 2 days after the administration of peramivir and initiate drug administration 2 weeks after vaccination.[64,77]

Laninamivir

Laninamivir has been available in Japan since 2010. It is a long-acting drug with a half-life of up to 74 h.[78] The recommended treatment is a single dose of 40 mg by oral inhalation in adults for the treatment of both influenza A and B infections. For prophylaxis, administration of 20 mg through inhalation on 2 consecutive days is recommended. Overall, laninamivir is well tolerated; the most frequently reported adverse reactions are cough, diarrhea, headache, and gastritis.[64]

Amantidine and rimantadine

Amantidine and rimantadine exhibit comparable efficacy and effectiveness in relieving or treating influenza A symptoms in healthy adults. However, rimantadine induces fewer adverse effects than amantadine. Amantadine was the first antiviral drug used against influenza, inhibiting its replication by blocking the influenza A-specific A/M2 proton channel.[64]

The efficacy of both drugs in interrupting transmission is low; moreover, there is significant resistance of influenza viruses to amantadine, particularly the new strains.[79,80] Both drugs have adverse gastrointestinal (stomach and intestinal) effects, while amantadine can also have serious effects on the nervous system. Renal function affects the excretion of these agents; thus, they should be administered according to the rate of creatinine clearance.[64] Hence, these drugs should only be used in emergencies, when all other measures fail.[81]

Baloxavir marboxil

Baloxavir marboxil represents the new generation of antivirals introduced in 2018. It is a long half-life (80 h) cap-dependent endonuclease inhibitor targeting influenza A and B viruses, including oseltamivir-resistant strains. It is administered orally within 48 h following symptom onset in a single dose of 40–80 mg, depending on the weight of the patient. The combination of baloxavirmarboxil with vaccination is not recommended.[64]

Pimodivir

Pimodivir is a novel cyclohexyl carboxylic acid analog inhibitor, targeting the early stages of viral replication by inhibiting the cap-binding function of the basic protein polymerase 2 (PB2) of IAVs.[82,83] Cell culture studies indicated that late addition of pimodivir at 6 h rapidly halts viral mRNA production and prevents cell death, unlike neuraminidase inhibitors tested under the same conditions.[84] Pimidivir inhibits a wide range of IAVs, including adamantane and neuraminidase inhibitor-resistant strains.[83,85] However, it exhibits limited or no activity against influenza B viruses.[84]

Pimidivir advanced to late-stage clinical development through phase 3 testing in hospitalized patients and high-risk outpatients with IAV infections.[84] Consequently, it was granted fast track designation by the US Food and Drug Administration.[82] However, in 2021, the manufacturing company announced that the clinical development of pimodivir had been halted “due to lack of benefit over the existing standard of care”.

1,3-dihydroxy-6-benzo [c] chromene(D715-2441)

The antiviral action of 1,3-dihydroxy-6-benzo [c] chromene (D715-2441) is attributed to the inhibition of influenza virus RNA polymerase activity by specific binding to the PB2 protein. This agent has demonstrated antiviral activity against several types of IAVs, including oseltamivir-resistant strains.[64]

FA-6005

FA-6005 is a new specific inhibitor targeting the IAV nucleoprotein, with pleiotropic inhibitory effects at several steps of the viral life cycle.[64] Hence, it is a promising candidate for further development as an antiviral drug for the treatment of influenza A infection.[86]

mAb

The emergence of resistance to currently available antiviral drugs emphasizes the need for the development of new therapies. Experimental administration of mAb was linked to increased survival, attenuation of histological changes, and a milder inflammatory response in the lungs. Several mAbs are currently in various stages of clinical development and, in the near future, may provide useful new tools against the rapidly evolving influenza virus.[87] The mAb are produced in laboratories, and demonstrate high specificity and homogeneity for the target antigen or epitope. Owing to the development of molecular biology, structural biology, and bioinformatics, mAb have undergone a series of technical advances to become a cornerstone of immunotherapy.[88]

In the last decade, several studies in humans revealed that mAb can bind and neutralize a wide range of influenza A and B viruses. Most of these mAb are directed against hemagglutinin, and some are currently under evaluation in clinical trials. Importantly, these clinical studies indicate that this approach is safe and can reduce influenza symptoms.[89] Nevertheless, the efficacy reported thus far has been limited. Researchers suggest that treatment should be initiated earlier (within 3–5 days) during the peak of viral replication.[90] This would require rapid diagnostic testing combined with the availability of mAb in the clinic. The objective parameters for assessing the results and their scoring warrant further investigation.[91] The pharmacodynamics of the fraction of systemically administered antibodies that reach the respiratory or nasopharyngeal epithelium remain unclear.[92] Of note, <1% of a biologic agent reaches the lung lumen, where the antibody may neutralize the virus and eliminate infected cells in cooperation with effector cells, such as macrophages and natural killer cells.[93] Pulmonary administration of anti-influenza antibodies could reduce the dose required and perhaps lead to a more pronounced clinical benefit.

Currently, the clinical use of mAb is expensive. Thus, there are ongoing attempts to develop more cost-effective methods for the production and administration of antibodies. Plant-derived mAb that can be rapidly and cost-effectively produced have been tested in human clinical trials.[94] Novel methods for expressing and/or delivering mAb, such as the delivery of mAb-encoding nucleotide sequences into the human body by DNA/RNA-based gene therapy or by adeno-associated viruses, are also under investigation.[95,96]

Corticosteroids

Initially, corticosteroids were administered empirically to decrease the inflammatory storm observed in patients with influenza infection. Subsequently, several studies showed that the use of corticosteroids was associated with an increased mortality rate, particularly when initially administered, and related to an increased incidence of nosocomial infections.

Recently, a phase 3, randomized, double-blind, multicenter, controlled trial [97] investigated the effects of intravenous hydrocortisone (200 mg daily for 4 days or 8 days as determined by clinical improvement) in 800 patients admitted to the ICU for severe community-acquired pneumonia. At day 28, the patients receiving hydrocortisone were at a lower risk of death compared with those receiving placebo. However, studies in patients with influenza and a recent meta-analysis [98] of 10 trials involving 6548 patients with severe influenza pneumonia showed that corticosteroid therapy was associated with a higher mortality rate, longer ICU stay, and an increased rate of secondary infection.

Therefore, the use of systemic corticosteroids is not recommended for the treatment of patients with influenza pneumonia in the ICU. However, this recommendation is based on a low level of evidence, highlighting the need for clinical trials. Some investigators suggest the administration of low-dose corticosteroids in the presence of septic shock, although the incidence is low in well-resuscitated patients. Expert guidelines also state that corticosteroids may be used in patients with ARDS after a course of antiviral treatment and a negative PCR test.[56,62]

Other treatments (statins, n-acetylcysteine, macrolide antibiotics, cyclooxygenase-2 inhibitors, etc.) intended to modulate the inflammatory response have been ineffective [99] (Figure 5).

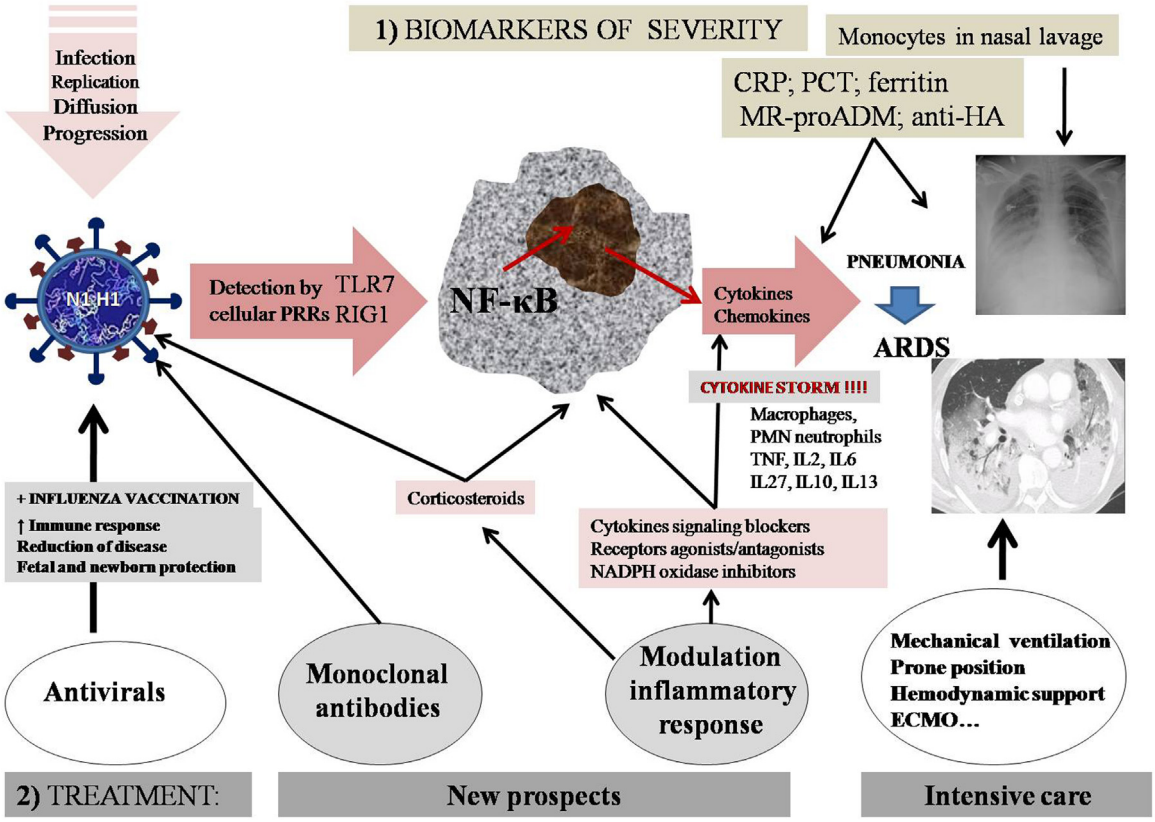

Figure 5. Sequence of inflammatory activation due to IAV infection and its evolution into pneumonia and/or ARDS. (1) Possibility of identifying biomarkers of severity in IAV infection. (2) Conventional treatment with antivirals, as well as respiratory and hemodynamic support. Possibility of new perspectives of treatment modulating the inflammatory response, generally or specifically, or the administration of monoclonal antibodies (adapted from Valenzuela-Sánchez et al.'s study[99] with permission from the authors).

ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; ECMO: Extracorporeal membrane oxygenation; HA: Hemagglutinin; IAV: Influenza A virus; IL: Interleukin; MR-proADM: Mid-regional proadrenomedullin; NADPH: Nicotinamide adenine dinucleotide phosphate; NF-κB: Nuclear factor-κB; PCT: Procalcitonin; PMN: Polymorphonuclear neutrophil; PRRs: Pattern recognition receptors; RIG1: Retinoid-inducible gene 1; TLR7: Toll-like receptor 7; TNF: Tumor necrosis factor.

Antibiotics

A review of the literature revealed great variability in the incidence of bacterial co-infection, which is partly explained by the heterogeneity of the studies and populations analyzed. The risk of bacterial co-infection in influenza pneumonia is increased in patients with H1N1vIPN. Therefore, it seems prudent to initiate empirical antibiotic treatment in these patients while simultaneously obtaining quality respiratory samples for microbiological study. This strategy allows the early withdrawal of antibiotic treatment in case of negative microbiological results. The rates of bacterial co-infection among patients with influenza infection are highly variable, presenting in the range of 2%–65% in different series.[36] It has been shown that biomarkers, such as PCT, are useful in ruling out the possibility of bacterial co-infection, especially in patients without shock, and may be useful in decision-making to discontinue antibiotic treatment.[100]

In reviews,[101] *Streptococcus pneumonia* and *Staphylococcus aereus* are the most frequently identified bacteria. This supports the use of empirical antibiotic treatment to cover these possibilities. Among the treatment options, ceftaroline is an effective anti-pneumococcal and anti-staphylococcal agent that also exhibits activity against methicillin-resistant bacteria.[102]

Antifungals

Influenza infection has been identified as a risk factor for invasive pulmonary aspergillosis in patients with severe pneumonia.[103] Based on this evidence, a group of investigators conducted a study of prophylaxis using posaconazole; however, the research did not yield conclusive results regarding the effects of treatment on mortality.[104] Therefore, it is of paramount importance to establish an active strategy for the detection of aspergillus infection in patients with severe influenza pneumonia. Such a strategy would ensure early and effective treatment.[105]

According to the Tarragona strategy, *Candida albicans* isolates(even when present in abundance) should not be treated with antifungals.[106] However, following the isolation of *Candida* in bronchoalveolar lavage or bronchial secretion samples obtained from patients with neutropenia and other risk factors (e.g., parenteral nutrition or corticosteroid treatment), the clinical situation should be reconsidered and antifungals should be administered. Moreover, the addition of antifungals to the treatment should be considered in the presence of fever and respiratory deterioration not explained by other causes, particularly in immunodepleted patients or those with hematological diseases.

Supportive measures

The basic supportive measure in this setting is the administration of oxygen (O_2) to correct hypoxemia and maintain O_2 saturation >90%. In case of pregnancy, O_2 saturation should be in the range of 92%–95%. In addition, it is important to maintain adequate hydration.[56]

O_2 therapy: non-invasive mv and high-flow nasal cannula (HFNC)

Provision of respiratory support is necessary when: (1) the administration of O_2 via nasal cannulae or mask is ineffective in maintaining O_2 saturation >90%; (2) the work of breathing is objectively maintained by tachypnea; (3) using the accessory musculature; or (4) a decrease in the base excess on blood gases is observed.[61,107]

Prior to MV, non-invasive MV is used without a scientific basis or proven benefit; this approach also involves a risk of aerosol generation for healthcare personnel.[108] Therefore, use of this method is not advisable because it delays scheduled intubation, thereby increasing the risk of requiring emergency intubation due to exhaustion with hypoxia and severe acidosis. Although its use has become widespread, there are also no favorable results on the use of a HFNC for O_2 administration in patients with H1N1vIPN. The ratio of oxygen saturation (ROX) index, which combines oxygenation (SpO_2/FiO_2) and work of breathing,[109,110] predicts the failure of $HFNCO_2$ therapy in patients with acute respiratory failure, particularly in those with COVID-19 pneumonia.[111,112] The ROX index might be clinically useful because it requires few data points and is easy to calculate at the bedside. Nevertheless, this index cannot replace close bedside observation of critically ill patients with respiratory failure. Furthermore, experience using this index in influenza is currently limited.[113] This index has not shown effectiveness compared with other indices in the early detection of treatment failure, need for intubation, and initiation of MV.[114] Therefore, the use of a HFNC is not recommended in these patients.[56]

Intubation/MV

Early intubation and MV constitute the basic treatment for severe respiratory failure. In severe influenza N1H1 pneumonia, the typical lung injury rapidly progresses to severe ARDS, characterized by a large radiological infiltrate and severe hypoxia.

Similar to the approach taken for other critically ill patients with sepsis, intubation should be performed using ketamine instead of etomidate.[115] It has been shown that MV with volumes of 6 mL/kg ideal weight reduces the mortality rate among patients who develop ARDS.[116,117] It is recommended to maintain a plateau pressure <30 cmH_2O, and to use moderate positive end-expiratory pressure<+10. Recruitment maneuvers should only be used in patients with refractory hypoxemia and a normalized preload. Sedation and relaxation levels should ensure correct synchrony between patient and ventilator.[118] Prone ventilation should be promptly performed in patients with ARDS.[118,119] A considerable proportion of patients will have prolonged MV; consequently, early tracheostomy should be considered.

A recent meta-analysis of studies involving >17,000 patients concluded that time to tracheostomy does not influence mortality or ICU or hospital stay.[120] Nevertheless, early tracheostomy is recommended in patients with respiratory distress syndrome and anticipated need for prolonged MV. Considering the unresolved debate on early or delayed tracheostomy, it is necessary not to limit research results to mortality outcomes but to consider other outcomes (e.g., the ability to communicate or eat), which may be of interest to patients.[121] Weaning in severe cases can be difficult, with persistent respiratory acidosis, pulmonary fibrosis, and frequent barotrauma, largely related to unnecessarily aggressive and demanding MV strategies.

ECMO

ECMO is an expensive technique and, thus, not available in most hospitals. Moreover, it is associated with serious complications, despite recent technical improvements. Studies have not shown any advantage in terms of mortality in patients with influenza infection.[122] Therefore, ECMO should be considered as an early rescue measure in cases of refractory hypoxia. Considering the lack of evidence pending the results of ongoing research, the experience of the medical team is an important factor that undoubtedly influences the rate of complications.

Fluids and hemodynamic monitoring

Apart from respiratory failure, hypotension and shock occur in approximately 55% of critically ill patients with influenza.[28] Hypotension is the initial clinical sign of impaired perfusion; however, it may co-exist with normal BP levels.[123,124] Although a non-specific parameter, plasma lactate is currently the best indicator of tissue perfusion. Persistently elevated levels of lactate in plasma are an important predictor of severity and mortality.[124] Other clinical signs, such as capillary filling in the skin and nails, persistent mottling of the skin, oliguria, or impaired consciousness, may also indicate a perfusion disorder. The mottling score is reproducible and easy to assess at the bedside.[125]

Lactate, central venous pressure, diuresis, and central venous O_2 saturation values should be routinely measured in the first hours of hospital treatment of patients with septic shock, regardless of the location. Despite its limitations, the central venous pressure is the most commonly used measurement.[126,127] In addition to providing a reference for preload and effective blood volume, central venous pressure measurements provide a “safety pressure threshold” for fluid intake in resuscitation. This is important because excessive fluid intake may be associated with subsequent oxygenation problems,[127] although it is not comparable to the problem of establishing high doses of vasopressors without completing proper fluid administration.[128] The amount of fluid and the time to improve perfusion in patients with septic shock are not well established; the time may exceed 24 h from symptom onset, and is independent of hemodynamic and metabolic components.[129]

An arterial catheter should be invasively inserted to monitor BP, because it is generally underestimated when assessed with an oscilloscope system.[130] Nonetheless, it is important to frequently check for system failures that may lead to errors in the BP and pressure waveform-derived parameters.[131] Importantly, central and arterial line cannulation should never delay the administration of fluids, blood cultures, laboratory tests, and antibiotic therapy.

Several methods of continuous monitoring can be used, which, together with bedside echocardiography, help to guide

treatment more accurately in the later stages, or when hypotension and respiratory failure are associated with normal plasma lactate levels.[128,132,133] Pulmonary artery catheterization should not be routinely used in patients with septic shock due to the increased risk of complications.[134]

Other measures

Other measures include enteral nutrition, prophylaxis against deep vein thrombosis, and renal replacement therapy.[135] Continuous renal replacement therapies and intermittent hemodialysis are equivalent for patients with severe sepsis and acute renal failure.

Conclusions

Influenza pandemics are unpredictable recurrent events with global health, economic, and social consequences.

Rapid management based on biomarker assessment is required to safely reach decisions regarding the admission of patients to the hospital or the ICU and ensure the provision of the necessary supportive care. Early implementation of treatment is important to increase effectiveness. All guidelines recommend the use of oseltamivir, based on a limited level of evidence. The possibility of drug resistance should be considered; in case of resistance, an agent should be replaced or a new-generation drug should be added to the treatment regimen. Adjunctive therapies with mAb are increasingly used against various viral infections. This is a promising strategy for improving outcomes in patients with influenza pneumonia. Corticosteroids should not be used in the initial treatment of these patients. Supportive measures are currently limited, with heterogeneous recommendations generated during the 2009 pandemic, and lacking recent updates.

The rapid spread of new influenza virus strains and drug resistance highlight the urgent need for new antiviral drugs and combination therapies with different mechanisms of action against alternative viral targets. There is an urgent need for clinical trials of antiviral treatment and respiratory support measures, as well as specific recommendations for different at-risk populations and research on the implementation of these guidelines in low-resource settings.

Author Contributions

Conceptualization: **Francisco Valenzuela-Sánchez** and **Ángel Estella**; Methodology: **Francisco Valenzuela-Sánchez**, **Ángel Estella**, and **Blanca Valenzuela-Méndez**; Formal analysis and investigation: **Francisco Valenzuela-Sánchez**, **Ángel Estella**, **Blanca Valenzuela-Méndez**, and **Juan Francisco Rodríguez-Gutiérrez**; Writing: **Francisco Valenzuela-Sánchez**, **Blanca Valenzuela-Méndez**, and **Ángel Estella**; Writing – original draft preparation: **Francisco Valenzuela-Sánchez** and **Ángel Estella**; Writing – review and editing: **Francisco Valenzuela-Sánchez** and **Ángel Estella**; Supervision: **Francisco Valenzuela-Sánchez** and **Ángel Estella**. All the authors contributed to interpretation of the data, critically revised the content, and gave final approval for publication.

Acknowledgments

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

None.

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