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Sepsis/Infection

Contemporary management of severe influenza disease in the intensive care unit

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ABSTRACT

Despite continued efforts to optimize vaccination composition, severe influenza disease requiring intensive care unit (ICU) admission remains a clinical issue. Influenza epidemics and pandemics worldwide continue to challenge clinicians with managing infected patients requiring ICU care. While routine use of antiviral therapy is deployed in ambulatory outpatients, their use in the ICU in patients with hypoxemic respiratory failure is less well established. Additionally, these therapies primarily target the neuraminidase protein, while contemporary research is increasingly demonstrating potential therapeutic benefits of targeting the hemagglutinin protein. These data have given rise to a growing interest in the use of immune modulating therapies for treatment of severe influenza. Additionally, pandemic outbreaks have revealed the growing need for salvage management, wherein lies the potential role for venovenous extracorporeal membrane oxygenation therapy in refractory respiratory failure. In this report, we review the contemporary ICU care of the severe influenza patient.

1. Introduction

Epidemics of influenza occur annually in the United States, typically between late fall and early spring. Surveillance data suggest influenza is responsible for nearly three quarters of a million hospitalizations, 100,000 intensive care unit (ICU) admissions, and over 25,000 deaths annually [1]. Children under two years of age and adults over the age of 65 years are at highest risk of adverse outcomes. Additionally, the presence of chronic medical conditions, immunosuppression, pregnancy, and obesity may also increase the risk of adverse outcome. The predominant seasonal influenza A virus subtypes in circulation since 1977 have been H1N1 and H3N2. However, since the 2009 influenza A H1N1 pandemic, the predominant seasonal influenza A is the 2009 H1N1 virus strain. It is this strain that has resulted in increased disease severity related to influenza.

Infection with influenza virus results in bronchial hyper-reactivity, distal airway obstruction, impaired diffusion capacity, and severe alveolar inflammation [2-4]. All of these factors lead to respiratory compromise and in severe cases the need for ICU admission and endotracheal tube placement to facilitate mechanical ventilation. The Centers for Disease Control and Prevention (CDC) recommends antiviral treatment as soon as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization [5]. Oseltamivir and zanamavir are recommended based on data indicating >99% of circulating strains are sensitive to these medications. Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified; however, the known impact has been limited. In this article we review approved and experimental therapies for adult patients hospitalized in the intensive care unit with severe influenza, a population at high risk for dismal outcome.

2. Antivirals

2.1. Oseltamivir

An inhibitor of the neuraminidase surface glycoprotein, oseltamivir has been the cornerstone of influenza treatment. A meta-analysis of randomized trials supports the use of oseltamivir in shortening the time to symptom alleviation, reducing the occurrence of lower respiratory tract infection, and admittance to the hospital with the only consequence being a higher risk of nausea and vomiting [6]. Furthermore, early oseltamivir use may reduce the duration of hospitalization in patients with influenza [7,8].

Randomized trials on the use and efficacy of oseltamivir have been conducted in patients who were not severely ill, wherein mortality

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would be rare. Therefore, evidence is limited which evaluates the impact of oseltamivir on mortality, an important endpoint in critically ill patients. As such, the use of oseltamivir in this patient population is based largely on observational reports. Many recent analyses have evaluated the impact of oseltamivir on influenza caused by the 2009 pandemic H1N1 strain.

The impact of early administration of oseltamivir was evaluated in a prospective, observational study of adult patients admitted to an ICU with microbiological confirmation of H1N1 infection during the 2009 influenza season in Spain [9]. The authors compared those patients who received early oseltamivir treatment (within 2 days of symptoms onset) to those who received oseltamivir >2 days after symptom onset. The effectiveness of early oseltamivir was evaluated with propensity scores created by using covariates determined among baseline differences between groups. This study evaluated 657 patients with a mean age of 44.7 ± 14.6 years. The mean APACHE II score on day 1 was 13.9 and 404 patients (61.1%) required invasive mechanical ventilation. In the entire population, 22.3% received early oseltamivir and more than half of these patients (68.8%) received oseltamivir 300 mg/day at ICU admission. In the entire patient population, there was a non-significant difference in ICU mortality between those who received early vs. late oseltamivr (OR 1.45; 95% CI 0.96–2.21). However, in a subset of patients ($n = 385$) on invasive ventilation who received effective treatment (defined as receiving >4 doses of antiviral therapy), ICU mortality was 34.3% in those receiving late oseltamivir and 21.3% in those receiving early oseltamivir (OR 1.9; 95% CI 1.06–3.41). The corresponding relative risk was 0.63 in those who received early oseltamivir (95% CI 0.40–0.99). Multivariable analyses confirmed the association of early oseltamivir with improved survival (OR for death 0.44; 95% CI 0.22–0.90) in this subset of ventilated patients. The authors concluded the early administration of oseltamivir was associated with improved survival in ventilated patients with 2009 H1N1 influenza.

A meta-analysis of individual patient data from multiple data sets sought to evaluate the efficacy of neuraminidase inhibitors (NAIs) in hospitalized patients during the 2009–10 influenza A pandemic [10]. The primary outcome was mortality during hospital admission or in the individual study follow-up period and the authors evaluated the effectiveness of oseltamivir in various subgroups of patients: treatment vs. none, early (within 2 days of symptom onset) vs. late treatment, early treatment vs. none, and late treatment vs. none. The authors were able to use 29,234 patients from 78 different data sets in their analysis, of which the mortality rate was 10%. Of these patients, 5103 were critically ill adults, defined as admission to a critical care unit, with a mortality rate of 70% in this patient population. Neuraminidase inhibitors were administered to 64% of patients in the entire population and oral oseltamivir was used in 92% of patients. Outcomes were adjusted for treatment propensity, corticosteroid use, and antibiotic use. Among critically ill adults, NAI use was associated with a mortality reduction compared to no therapy (OR 0.72; 95% CI 0.56–0.94). Early NAI use was associated with a reduction in mortality compared to late therapy (0.62; 95% CI: 0.49–0.77) in critically ill patients. The mortality reduction was also statistically significant for critically ill patients who received an NAI versus no therapy in those treated earlier (OR 0.31; 95% CI 0.20–0.47) and later (OR: 0.65; 95% CI 0.46–0.93). The study is limited by the inability to control for disease severity at baseline; however, the large dataset provides evidence that use of NAIs is associated with reduced mortality in critically ill patients.

This data would support that oseltamivir is associated with reduction in mortality when used early in patients with pandemic H1N1 influenza. However, even when not used early, late oseltamivir use may also be associated with reductions in mortality. Median time from symptom onset to late oseltamivir was 4.5 days in the study by Rodriguez et al. and 4 days in the study by Muthuri et al. The effectiveness of oseltamivir in patients presenting outside this window is not entirely clear. There are many limitations to the interpretation of this data in critically ill patients including lack of standard definitions for critically ill patients and lack of evaluation of differences in outcome in those with or without a history of underlying pulmonary disease or concomitant bacterial pneumonia which are associated with increased morbidity [4]. Furthermore, it's unclear whether the potential benefits of NAIs seen in these studies would also apply to patients with non-pandemic strains of influenza or whether these benefits would be seen in vaccinated vs. unvaccinated patients. This is of importance as prior studies have demonstrated that influenza vaccination may protect against secondary pneumonia, but this may be dependent upon the circulating influenza strain [11]. Oseltamivir is generally well-tolerated; however, neuropsychiatric events such as delirium, hallucinations, and behavioral changes or rare dermatologic reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome) have been reported and may discourage use in critically ill patients.

2.1.1. High-dose oseltamivir

There has been interest in using doses of oseltamivir that are higher than the standard recommended 75 mg twice daily dose. This interest has been born out of concerns regarding absorption of oseltamivir in critically ill patients and perhaps improved efficacy of the higher dose. A pharmacokinetic study sought to evaluate plasma concentrations of oseltamivir administered orally or via nasogastric tube in critically ill patients with H1N1 [12]. Serum levels of oseltamivir free base and its carboxylate metabolite were measured at baseline and then 2, 4, 6, 9, and 12 h after the fourth oseltamivir dose or later. Of the 41 included patients, 73% received enteral nutrition and 32% were on vasopressor therapy. The authors found serum concentrations of active oseltamivir carboxylate metabolite that were similar to levels seen in ambulatory patients. Therefore, it is likely trough concentrations were above the theorized pharmacodynamic threshold for maximal inhibition of the virus, though the authors did not report these values. Furthermore, there was no correlation between body weight and area under the curve for volume of distribution suggesting dose adjustments are not required for obesity.

A retrospective cohort study in 123 critically ill patients receiving either high-dose (>150 mg/day) or standard dose (≤150 mg/day) oseltamivir based on a renally adjusted daily dose to evaluate the impact on ICU-free days [13]. Patients who received the higher dose ($n = 77$) were younger (52.7 vs. 60.4 years), had a higher SOFA score on day 1 of therapy (7 vs. 5), had a higher fraction of inspired oxygen on day 1 of therapy (75% vs. 51%), and were more likely to have influenza A (78% vs. 54%). Other baseline characteristics and use of other therapies such as vasoactive medications and antibiotics were similar between groups. Patients who received high dose oseltamivir had fewer ICU free days (2 vs. 16.5, $p = .015$), ventilator-free days (10 vs. 22, $p < .01$), and had higher 28-day mortality (39% vs. 15.2%, $p < .01$). In multivariable analyses, high-dose oseltamivir was not independently associated with mortality or time to ICU discharge. This study does not support differences in clinical outcomes with high-dose oseltamivir.

A randomized, controlled trial conducted in Indonesia, Singapore, Thailand, and Vietnam compared double dose oseltamivir (150 mg twice daily) to standard dose oseltamivir (75 mg twice daily) [14]. The primary endpoint was the absence of viral RNA in a combined nasal and throat swab on day 5. The study included both pediatric and adult patients and doses of oseltamivir were adjusted in those weighing <40 kg. All patients received five days of oseltamivir, while those meeting criteria for clinical failure at day 5 received an additional five days of therapy. The majority (246/326, 75%) of enrolled patients were children with a median age of 2 years. Influenza A was present in 260 (79.8%) patients, 133 (40.8%) with A/H3N2, 72 (22.1%) with A/H1N1 pdm09, 38 (11.7%) with seasonal A/H1N1, and 17 (5.2%) with A/H5N1. ICU admission was required in 57 (17.5%) patients and 34 (10.4%) required mechanical ventilation. At day five, the proportion of patients with a negative viral RNA was similar between the double dose (72.3%) and standard dose (68.2%) groups ($p = .42$). Between the double dose and standard dose groups, there was also no difference in clinical failure at day 5 (9.9% vs. 13%, $p = .44$) or mortality (7.3% vs. 5.6%, $p = .54$). The

majority of deaths were in patients with avian H5N1 virus. This study does not support differences in clinical or virologic outcomes when higher doses of oseltamivir are used, although these results can only be primarily applied to the pediatric population.

Limited data exist regarding absorption of oseltamivir and drug concentrations in critically ill patients with one pharmacokinetic study suggesting drug concentrations obtained in critically ill patients do not differ from ambulatory patients as described above [11]. Furthermore, there is no evidence to suggest differences in clinical outcomes based on oseltamivir dose. Oseltamivir 75 mg orally twice daily (adjusted for renal function) may be used in the majority of critically ill patients, unless significant malabsorption is known or suspected.

Given the disease severity associated with influenza-related illness encountered in the ICU, many patients may eventually require renal replacement therapy or extracorporeal membrane oxygenation (ECMO). A prospective pharmacokinetic study of 13 patients on either continuous venovenous hemodiafiltration (CVVHD) or ECMO evaluated the pharmacokinetic parameters and plasma concentrations of oseltamivir in these patients [15]. All patients in this study received oseltamivir 150 mg twice daily. Serum samples were obtained at regular intervals following drug administration just before the hemodialyzer (CVVHD) or directly before and after the oxygenator (ECMO). CVVHD contributed significantly to the clearance of oseltamivir carboxylate while pre- and post-oxygenator concentrations of oseltamivir and oseltamivir carboxylate did not differ. The authors found a higher oseltamivir carboxylate area under the curve for the 12-hour dosing interval (AUC_{0-12}) than would be expected in non-critically ill patients receiving the same dosage regimen. The dose utilized resulted in higher median AUC_{0-12} levels than would be expected in non-critically ill patients receiving the same regimen. The authors stated the 75 mg twice daily dose of oseltamivir would be reasonable in patients on CVVHD at similar effluent rates to those used in this analysis (3300 ± 919 mL/h). Furthermore, AUC_{0-12} was lower in patients receiving both CVVHD and ECMO compared to patients receiving only CVVHD. The study population may have been too small to draw firm conclusions regarding oseltamivir dosing in ECMO; however, the authors speculated that higher dose may be required in these patients, particularly when gastrointestinal dysfunction may be present.

2.1.2. Duration of therapy

Oseltamivir duration of therapy beyond five days has not been formally evaluated, but has been recommended by clinical experts. During the 2009 H1N1 pandemic the World Health Organization (WHO) recommended that antiviral therapy be maintained until satisfactory clinical improvement [16]. The CDC echoed this recommendation for prolonged therapy in patients in whom a severe state continued beyond five days [5]. Prolonged viral shedding has been noted to be present beyond the 5–7 days in hospitalized patients with influenza [17]. Given the lack of clinical data, it may be reasonable to extend the duration of oseltamivir beyond five days in patients with severe influenza and delayed clinical response. Alternatively, if readily available, antiviral drug susceptibility testing may be considered.

2.2. Peramivir

The FDA Commissioner ordered an Emergency Use Authorization (EUA) for intravenous peramivir during the 2009 influenza season [18]. The drug could be accessed for hospitalized patients with suspected or confirmed H1N1 influenza. Peramivir received approval by the FDA in 2014. Approval was based on a multinational, multicenter, double-blind, double-dummy randomized controlled study in which patients received a single intravenous infusion of peramivir (300 or 600 mg) or oral oseltamivir (75 mg twice daily for 5 days) [19]. In this study, peramivir was found to be non-inferior to oseltamivir in regards to alleviation of influenza symptoms.

Following the EUA for intravenous peramivir, initial evaluations of patients who received the therapy demonstrated that the drug was well tolerated and associated with recovery in most patients [20]. Rash was the only treatment-related adverse effect attributable to peramivir in an analysis of reports submitted to the FDA Adverse Event Reporting System [18].

An analysis of hospitalized ICU patients in California sought to describe the epidemiology, clinical characteristics, and outcomes of patients who received IV peramivir during the 2009 H1N1 epidemic [21]. Cases were those patients hospitalized in an ICU for ≥24 h with acute respiratory infection and laboratory evidence of H1N1 infection by reverse-transcriptase polymerase chain reaction. A comparative analysis was performed in critically ill patients treated with NAIs, but who did not receive peramivir. Of 1684 patients who received treatment with an NAI, 57 (3%) received IV peramivir. Of these 57 patients, 95% were on mechanical ventilation and 25% had suspected bacterial co-infection. The majority of these cases received a concurrent second antiviral, most commonly oseltamivir. Time from symptom onset to treatment with an oral NAI was 4 days and from symptom onset to peramivir was 9 days. The most common reasons for initiation of peramivir were "not responded to oral or inhaled antivirals" (75%) and "suspected malabsorption" (12%). Twenty-nine patients (51%) who received peramivir died. Patients who died after receiving peramivir were more likely to be diagnosed with acute renal failure ($p = .02$), have a shorter length of hospital stay (16 vs. 31 days; $p = .002$), and receive peramivir for a shorter duration (7 vs. 9 days; $p = .02$) compared to survivors who received peramivir. Patients who received peramivir were compared to 1627 cases in the ICU treated with NAIs, but not peramivir. Patients treated with peramivir had a higher rate of obesity and morbid obesity, and were more likely to be diagnosed with pneumonia/acute respiratory distress syndrome (ARDS) ($p = .0002$) or sepsis ($p < .0001$), to require mechanical ventilation ($p < .0001$), and to die ($p < .0001$). The authors questioned the safety and effectiveness of peramivir in hospitalized critically ill patients and highlighted the need for large randomized controlled trial in this area.

A single-institution retrospective review conducted in Korea sought to compare the efficacy of peramivir and oseltamivir in critically ill patients with seasonal influenza [22]. Critically ill patients were defined as those admitted to an ICU or requiring mechanical ventilation with a PaO_2:FiO_2 ratio < 300 and who required infusion of an inotropic or vasoactive medication. Patients were divided into two groups based on initial treatment with either peramivir ($n = 34$) or oseltamivir ($n = 26$). The average age was 68 years and 55% were male. At baseline, patients who received peramivir had a higher SOFA score (11 vs. 8.5) and a higher proportion of patients were in shock (64.7% vs. 38.5%). Patients who received oseltamivir were more likely to have chronic heart disease (38.5% vs. 8.8%). Influenza A was predominant in both groups with 85.3% in the peramivir group and 88.5% in the oseltamivir group. Peramivir was changed to oseltamivir in 15 patients (44.1%), primarily due to clinical improvement while in the ICU. Oseltamivir was changed to peramivir in 13 patients (50%) and eleven of these patients had progression of pneumonia. Half of patients treated with peramivir received a 600 mg dose while 65.4% of oseltamivir patients received a 75 mg dose. The median duration of antiviral therapy was 9.5 days in the peramivir group and 11 days in the oseltamivir group. Between the peramivir and oseltamivir groups, there was no difference in ICU mortality (38.2% vs. 30.8%; $p = .548$), in-hospital mortality (44.1% vs. 38.5%; $p = .660$) or ICU or hospital length of stay. In multivariate analysis increasing age was associated with 28-day mortality, but peramivir use was not. The authors concluded that critically ill patients with severe influenza can be treated with either intravenous peramivir or enteral oseltamivir depending on the most appropriate route of administration with no difference in outcomes; although the study may have lacked adequate power to detect differences in these outcomes.

A case-series in Taiwan described the use of salvage peramivir in 71 critically ill patients who had initially received oseltamivir or peramivir [23]. Time from symptom onset to oseltamivir was 4.6 days and time from onset to peramivir was 8.6 days. There was no difference between

survivors and non-survivors on time to receipt of either oseltamivir or peramivir. Overall survival was 62% (44/71) and was 59.6% (34/57) in adult patients. In multivariate logistic regression analysis of 57 adult patients, lower body weight, complications with bacteremia, acute renal injury, and higher steroid use were independent predictors of mortality. The authors recommended further studies to evaluate the safety and efficacy of peramivir.

Further study is needed in critically ill patients to evaluate the efficacy of peramivir. At this time, there is a lack of compelling evidence to recommend peramivir over oseltamivir; however, it may be considered in patients who are unable to receive oral oseltamivir. As with oseltamivir, neuropsychiatric or rare dermatologic reactions may occur.

2.3. Zanamivir

Data on the use of zanamivir in critically ill patients is much more limited than with oseltamivir and peramivir. The only approved formulation of zanamivir is an inhaled dry power delivered via a diskhaler device. Aerosolized zanamivir is not recommended in critically ill patients on mechanical ventilation as it may clog the ventilator circuit. Intravenous zanamivir is an investigational product only available via enrollment in a clinical trial or under an investigational new drug request. Strains of H1N1 during the 2013–2014 and 2014–2015 influenza seasons showed >98% susceptibility to oseltamivir and peramivir; however, 100% of these strains were susceptible to zanamivir [24]. Zanamivir appears to maintain activity against oseltamivir-resistant and peramivir-resistant influenza strains. There is limited data to guide the use of IV zanamivir in critically ill patients.

An international phase III study of intravenous zanamiavir in hospitalized patients with influenza compared intravenous zanamivir (300 mg or 600 mg) to oral oseltamivir [25]. At baseline approximately 40% of patients were in the ICU and 17% required endotracheal intubation, and half of patients received prior treatment with oseltamivir. There was no difference in time to clinical response in the entire population or in the population of patients admitted to the ICU.

Other case reports or case series describe the use of intravenous zanamivir in critically ill patients [26,27]. These reports describe use of intravenous zanamivir in critically ill patients who have had disease progression despite oseltamivir. The use of zanamivir led to clinical success in the majority of patients; however it is difficult to draw firm conclusions with such limited data. It may be reasonable to use intravenous zanamivir through FDA investigational new drug request process in patients who have confirmed or suspected oseltamivir-resistant or peramivir-resistant strains.

2.4. Triple antiviral therapy

Data regarding the use of adamantane antiviral agents—targeting the M2 protein ion channel—are restricted to the non-critically ill population, and monotherapy with these agents has largely fallen out of favor given the high propensity for resistance. There are however limited data evaluating amantadine as part of a triple drug therapy approach [28,29]. Kim et al. retrospectively analyzed a cohort of 127 patients who required mechanical ventilation during the 2009 H1N1 pandemic in Korea. Twenty four of these patients received treatment with combination oseltamivir 150 mg twice daily, amantadine 100 mg twice daily, and ribavirin 300 mg thrice daily and 103 received oseltamivir monotherapy [28]. While there were no significant adverse safety concerns, the authors found that triple antiviral therapy did not reduce mortality and overall outcomes were similar to those who received just oseltamivir monotherapy. No virologic endpoints were assessed in this study. In a double-blinded fashion, Beigel et al. randomized patients to receive triple therapy with oseltamivir 75 mg twice daily, amantadine 100 mg twice daily, and ribavirin 600 mg twice daily, or oseltamivir monotherapy [29]. While the authors found greater viral clearance with triple therapy, clinical endpoints including resolution of symptoms were no different from monotherapy. Unfortunately, the authors did not report how many persons required ICU admission or mechanical ventilation, limiting the ability to extrapolate this data to the critically ill population.

3. Immunomodulating therapies

Historical influenza pandemics have served as the backbone of research and advancement in the management of severe influenza disease [30]. Kobasa and colleagues used reverse genetics to synthesize the hemagglutinin (HA) and neuraminidase (NA) genes present in the influenza virus responsible for the 1918 Spanish influenza pandemic [31]. They infected three different mouse models, one with wild-type virus, one with both 1918 engineered HA and NA genes, and one with just the 1918 HA gene. While the wild-type model experienced mild disease and minimal pathological changes, both mutant models manifested diffuse pulmonary disease, massive cytokine surge, and alveolar hemorrhage. Because these pathological changes were present in both models, irrespective of neuraminidase changes, the authors suggest that mutations in the hemagglutinin gene alone are the primary drivers for virulence of the virus.

As such, several mechanisms of benefit of immune modulating therapies on severe influenza disease have been proposed. Anti-influenza antibodies may (1) inhibit the binding of virus to sialic acid receptors on epithelial cells lining the respiratory tract, (2) inhibit protease activation of hemagglutinin, (3) inhibit viral fusion to epithelial cells and subsequent internalization of virus, and (4) prevent the release of progeny virions from host cells [32].

3.1. Convalescent plasma

The use of convalescent blood products for infectious diseases dates back to the 1800s wherein their use was routine for the treatment and prevention of bacterial and viral infections. While their use tapered off with the discovery and widespread use of antimicrobial agents in the early-mid 1900s, convalescent products continue to be used today for severe viral illnesses that lack vaccination, medications, or other specific therapies such as those due to Ebola virus disease, Middle East respiratory syndrome coronavirus, SARS coronavirus, and others [33].

Observational experience from the 1918 Spanish influenza pandemic found mortality benefit with the use of convalescent plasma, particularly when administered early in the course of illness [34]. In the modern era, convalescent plasma was first administered to an otherwise healthy middle-aged male in the Guangdong province of China with 2006 H5N1 who did not respond to standard oseltamivir therapy [35]. The plasma was collected from a patient who suffered from H5N1 influenza disease in the Anhui province earlier that year. The hemagglutinin genes of the two viruses shared near complete homology. Shortly after administration, the patients' viral load decreased precipitously to undetectable levels and his fevers resolved. This case suggests convalescent product need not be collected from patients who suffered from the exact same strain of influenza virus, which may be beneficial in commercializing its use.

A prospective cohort study of 93 patients during the 2009 H1N1 pandemic evaluated those who deteriorated despite optimal antiviral treatment and required ICU admission within 7 days of their symptom onset [36]. Twenty (21.5%) patients received treatment with convalescent plasma. Nearly all patients required mechanical ventilation, almost half received stress dose steroids, and approximately one-eighth were placed on ECMO. Multivariable analysis revealed treatment with convalescent plasma was independently associated with survival (9% dead vs. 33% alive, $p = .01$). Additionally, viral loads and inflammatory markers including IL-6, IL-10, and TNF-α, decreased at a higher rate in those who received convalescent plasma.

The first and only randomized controlled trial of convalescent plasma enrolled patients with severe influenza disease defined by

hypoxia (arterial oxygen saturation < 93%) and tachypnea (respiratory rate > 20 bpm) [37]. Approximately one-half of the entire cohort was infected with H3N2 and over a third with H1N1. Patients were randomized to receive convalescent plasma or no convalescent plasma. Both groups received standard of care which included antiviral therapy, most commonly oseltamivir. Nearly all included patients required oxygen administration in some form, over one-third were diagnosed with the acute respiratory distress syndrome, and over half required ICU admission. While there was no difference in the primary outcome between the groups which was normalization of respiratory status, subgroup analysis revealed significant benefit in those patients who received plasma within 4 days ($p = .038$). No differences were found in ICU admission, ICU or hospital length of stay, need for mechanical ventilation or supplemental oxygen, or adverse events.

This study was however underpowered and un-blinded which may have led to higher rates of lack of follow-up among those randomized to the standard of care arm. Both groups received NAIs and thus the true effects of convalescent plasma on influenza disease remain unknown. Because of the variability in hemagglutinin inhibition titers among plasma administered, the effective dose remains unknown. To address many of these limitations, a Phase III, double-blind, randomized trial of high- vs. low-titer convalescent plasma for severe influenza disease is currently ongoing (NCT02572817).

Safety considerations with the use of convalescent plasma include those expected with the administration of blood product such as transfusion-related reactions, transfusion-related lung injury, antibody-dependent enhancement, blood borne infection, and thromboembolic disease [34]. Additionally, due to the higher volume load, some patients may not tolerate plasma infusion.

3.2. Intravenous immunoglobulin

Created from pooled sera from thousands of donors, intravenous immunoglobulin (IVIg) was originally thought to contain anti-influenza antibodies. Additionally, studies have suggested IgG benefits of IVIg beyond specific anti-influenza antibodies. These include IVIg containing (1) large amounts of carbohydrate-binding antibodies which may shield sialic acid binding sites on respiratory epithelial cells and (2) sialylated portions serving as decoys for influenza viral binding [38].

Experience with IVIg for influenza disease is limited to a case report of an otherwise healthy male necessitating mechanical ventilation during the 2009 H1N1 pandemic [39]. Despite high-dose oseltamivir therapy, his ventilatory requirements continued to increase and thus IVIg was administered at a dosage of 400 mg/kg daily for 5 days. Approximately a week following the first dose of IVIg, he was able to be liberated from the ventilator.

An analysis of commercially available IVIg products revealed increasing HA and microneutralization titers with increasing IVIg concentrations [40]. These authors found that after administration of high dose IVIg (2 g/kg), serum titers of microneutralization and HA were significantly increased. Caution should be executed with these data however, as the level of hemagglutinin inhibition present in commercially available IVIg products may be dependent on geographic location and the demographic of patients selected as serum donors.

3.3. Hyperimmune globulin

Due to the shortcomings of IVIg, hyperimmune globulin (hIVIg)—created from fractionation of convalescent blood products—is proposed to confer all of the same IgG benefits of IVIg with added specific anti-influenza antibodies. The INSIGHT FLU group performed a pharmacokinetic analysis of HA inhibition evolution with hIVIg [41]. After administration of hIVIg to patients with active influenza disease (mainly 2013 H1N1 pdm09 or influenza B), serum HA inhibition titers were significantly increased at least three days earlier than those patients administered placebo undergoing the natural course of infection.

A randomized, double-blind trial evaluated 35 patients with 2009–2011 H1N1 who deteriorated despite standard antiviral treatment requiring ICU admission and positive pressure ventilation within 7 days of their symptom onset [42]. Patients were randomized to receive hIVIg (400 mg/kg) or IVIg (400 mg/kg), of which the IVIg screened for use was required to have low levels of HA inhibition titers. Nearly all (94%) of the included patients required mechanical ventilation, and over a third were placed on ECMO. Viral loads were significantly reduced at 5 and 7 days in hIVIg recipients. When administered within 5 days of symptom onset, hIVIg conferred significantly greater survival benefit over IVIg recipients ($p = .04$). This study was limited by its small sample size and high number of excluded patients for late ICU admission. Long term outcomes and the ideal dosage of hIVIg remain unknown. To address many of these limitations, a quadruple-blind, randomized trial of hIVIg with or without standard antiviral therapy for severe influenza disease is currently ongoing (NCT02287467).

Safety considerations for IVIg and hIVIg must be extrapolated from their use in other indications due to lack of available data in influenza disease. Adverse events include those expected with immunoglobulin administration such as infusion-related reactions, acute kidney injury, thromboembolic disease, hemolytic anemia, and anaphylaxis [43,44].

Despite a lack of direct comparisons, convalescent plasma appears to be the most promising anti-influenza antibody therapy, particularly in a pandemic scenario due to novel influenza strains. IVIg's lack of specificity for influenza and hIVIg's time-consuming production may limit their utility in pandemic influenza outbreaks. Nonetheless, significant hurdles remain with limited clinical outcome data and methods for mass production and commercialization potentially limiting convalescent plasma's ability for widespread use currently as production must be outsourced to specialty biomedical laboratories and is highly dependent upon the availability of willing donors [45].

3.4. Corticosteroids

Due to the propensity for severe pulmonary inflammation and respiratory decompensation in influenza disease, corticosteroids are suggested to confer immunomodulatory benefit. Several studies have evaluated corticosteroids for influenza disease without promising results.

Martin-Loeches et al. performed a prospective observational study during the 2009 H1N1 pandemic evaluating corticosteroid use in 220 patients admitted to the ICU [46]. Approximately 70% required mechanical ventilation and nearly a third died in the ICU. Patients who received steroids were more likely to die in the ICU (46.0% vs. 18.1%, $p < .01$), however they were older and more likely to have prior pulmonary disease. Despite this, adjusted analyses revealed no differences in mortality, though rates of hospital-acquired pneumonias were higher in steroid recipients (OR 2.2, $p < .05$). In another study during the 2009 H1N1 pandemic, Brun-Buisson et al. showed no clinical benefits from steroid use in a population with ARDS, but ICU-acquired pneumonia was nearly double in steroid recipients (41% vs. 26.4%, $p = .01$) [47]. Furthermore, Kim et al. also found higher rates of superinfection in their steroid recipients during the 2009 H1N1 pandemic [48]. Finally, in a cohort of 147 hospitalized patients infected with 2007 H3N2, Lee et al. found corticosteroids were associated with delayed viral clearance (adjusted OR 5.44, 95% CI 1.86–15.89) [49].

Strikingly, many of the studies evaluating effects of corticosteroids found increased risk of death with their use, even after adjustment for confounding factors [47,48,50]. Overall, corticosteroids for influenza disease lack clinical benefit, appear to be detrimental, and their use should be discouraged.

3.5. Macrolides

The host immune response to influenza infection may play a critical role in disease severity. Pro-inflammatory cytokines, such as

interleukins and tumor-necrosis factor, are highly expressed and are mediators of tissue inflammation contributing to increase disease severity and poor outcomes. Macrolides are known to possess anti-inflammatory properties and may be able to alleviate symptoms and improve outcomes in patients with pro-inflammatory diseases, such as influenza. A study of hospitalized patients with mainly 2013–2015 H3N2 infection evaluated the anti-inflammatory effects of azithromycin combined with oseltamivir compared to oseltamivir alone [51]. In patients receiving azithromycin, significant anti-inflammatory effects were noted supporting additional trials evaluating clinical benefits.

An open-label clinical trial with randomized treatment group assignments in Hong Kong compared the three-drug combination of clarithromycin-naproxen-oseltamivir with oseltamivir alone in hospitalized patients with influenza A (2015 H3N2) [52]. In the experimental group ($n = 107$), clarithromycin 500 mg, naproxen 200 mg, and oseltamivir 75 mg were given twice daily, followed by oseltamivir 75 mg twice daily for an additional three days. The control group ($n = 110$) received oseltamivir 75 mg twice daily for 5 days. All patients also received 1 g of amoxicillin-clavulanate twice daily for 5 days. The primary outcome was 30-day mortality. The median age was approximately 81 years and very few patients appeared to have severe disease as <20% required invasive or non-invasive ventilation during hospitalization and only 9 patients were admitted to the ICU. Nevertheless, 30-day mortality was reduced in the experimental group (0.9% vs. 8.2%, $p = .01$) and the experimental therapy was the only independent factor associated with lower 30-day mortality in multivariate analyses. The findings from this clinical trial are certainly interesting; however, its unknown if the therapy would be beneficial in a sicker population or in patients with different influenza strains. In addition, the use of naproxen may be relatively contraindicated in critically patients who are already at high risk of acute kidney injury.

The use of macrolide-based treatment was examined in a secondary analysis of a prospective, observational study of critically ill patients with H1N1 influenza conducted in Spain during the 2009 pandemic [53]. The need for antibiotic therapy was at the discretion of the treating physician. Primary viral pneumonia was present in 733 patients and 190 of these patients were administered macrolides, usually in combination with other antimicrobial agents. Clarithromycin was utilized in 99 patients, azithromycin in 90 patients, and erythromycin in one patient. In patients who did not receive a macrolide ($n = 543$), 451 patients (83.1%) received double combination antibiotic therapy and 57 (10.5%) received triple combination therapy. Overall ICU mortality was 24.1% and was lower in patients who received macrolides compared to those who did not (19.2% vs. 28.1%, $p = .02$). In a logistic regression analysis controlling for APACHE II score and potential confounding factors, macrolide use was not associated with significant reductions in mortality (OR 0.89; 95% CI 0.53–1.49). Similar results were obtained in a subgroup of patients on mechanical ventilation. The results do not suggest a benefit of macrolide treatment in critically ill patients with primary viral pneumonia due to H1N1.

At this time there is a lack of strong compelling data to suggest initiation of a macrolide antibiotic to improve outcomes in patients with influenza; however, this therapy may be frequently utilized in patients with concomitant pneumonia.

3.6. Mammalian target of rapamycin inhibitors

The immune system cascade activated in response to influenza infection may be a potential therapeutic target. Wang et al. suggest mammalian target of rapamycin (mTOR) inhibitors may inhibit T cell activation, providing a protective effect in terms of the cytokine storm induced by the virus [54]. These authors performed an open-label prospective trial, wherein patients with PCR-confirmed influenza (2009–2011 H1N1) and respiratory support requiring mechanical ventilation ($n = 38$) were randomized to standard oseltamivir therapy with or without sirolimus 2 mg/day. Both groups also received corticosteroids at a standardized 20 mg/day dose of prednisolone. They found more favorable PaO_2:FiO_2 at day 3 and 7, and quicker liberation from mechanical ventilation among sirolimus recipients. Sirolimus recipients also had a greater proportion of patients with negative repeat PCR at day 7 (75% vs. 33%, $p < .05$), however quantitative assessments were not performed. No differences in the need for ECMO or death were observed. Given their undesirable adverse effects including cytopenias and renal injury, among others, more robust studies need to be performed to substantiate these findings prior to their widespread use.

4. Extracorporeal membrane oxygenation

Despite its high mortality when initially conceived in the 1950s, ECMO as an adjunctive therapy for severe influenza disease skyrocketed during the 2009 H1N1 pandemic [55]. Due to severe respiratory failure and refractory hypoxemia, ECMO may augment respiratory efforts allowing the ability for lung recovery during treatment of influenza disease.

Use across Australia and New Zealand during the 2009 H1N1 southern-hemisphere winter pandemic described 61 ECMO recipients as young and healthy at baseline, with minimal comorbidities [56]. Prior to ECMO initiation, recipients were severely ill with lowest median PaO_2/FiO_2 ratios of 56, highest median $PaCO_2$ of 69 mmHg, and a median acute lung injury score of 3.8. Those who received ECMO spent nearly twice as long on the mechanical ventilator (18d vs. 8d, $p < .001$) and in the ICU (22d vs. 12d, $p < .001$), and were twice as likely to expire in the ICU (23% vs. 9%, $p = .01$) compared to those who were mechanically ventilated without ECMO. Despite their high severity of illness from influenza and the acute respiratory distress syndrome, ECMO recipients had a mortality rate of only 21%.

A report from the United Kingdom during the 2009 H1N1 northern-hemisphere pandemic described a cohort of 80 patients referred for ECMO with similar baseline demographics and slightly higher severity of illness with marginally greater use of vasoactive support and renal replacement modalities in ECMO recipients [57]. Mortality was modestly higher at 27.5%, however when propensity-matched to non-ECMO patients, ECMO recipients were less likely to die (24% vs. 46.7%, $p = .008$). Similarly, subsequent meta-analysis found an overall random-effects pooled mortality rate of 28% across 8 studies of 266 ECMO recipients [58]. Contrarily, a recent study found higher and similar mortality rates between their propensity-matched ECMO recipients and non-recipients (50% vs. 40%, OR 1.48, $p = .32$) [59].

Overall ECMO experience in severe influenza disease appears to be greatest among the young, otherwise healthy population who manifest very severe disease. Until more information is available regarding optimal timing of cannulation, ECMO appears to be a viable salvage therapy in patients suffering from severe influenza illness with refractory hypoxemia, particularly during pandemic scenarios.

5. Conclusion

Influenza is a significant source of morbidity and mortality in the ICU. Much of the care provided is supportive in nature; however, evidence suggests that early use of neuraminidase inhibitors (NAI) may be associated with mortality reduction in critically ill patients. Strategies to enhance NAI performance, including use of double dose oseltamivir and development of alternative agents such as intravenous peramivir, have failed to show benefit in the ICU population. Immune modulating therapies have shown promise in the limited available evidence. These agents may be particularly useful in pandemic scenarios due to novel influenza strains, specifically in patients failing to improve despite standard therapy and escalating respiratory support. However, larger scale randomized controlled trials of these therapies and optimization of the manufacturing processes and commercialization of these products is necessary for their successful widespread application.

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Appendix A. Supplementary data

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