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Influenza A (H1N1) virus-associated acute respiratory distress syndrome: the potential role of extracorporeal membrane oxygenation in pandemic level treatment

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INFLUENZA A (H1N1) VIRUS-ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME: THE POTENTIAL ROLE OF EXTRACORPOREAL MEMBRANE OXYGENATION IN PANDEMIC LEVEL TREATMENT

by

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DEDICATION

This thesis is dedicated to the many lives lost and affected by the 2009 Influenza A (H1N1) pandemic and the researchers who remain dedicated to the prevention and care of respiratory illnesses across the globe.

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ABSTRACT

The 2009 Influenza A (H1N1) virus quickly became a pandemic and a threat to the health of many across the globe. H1N1 was able to preferentially bind to pneumocytes in the lower lung, resulting in atelectasis, surfactant disruption, and eventual acute respiratory distress syndrome (ARDS). Management of ARDS during this time included non-ventilatory and ventilatory techniques such as conservative fluid management, prone positioning, differing PEEP levels, and Extracorporeal Membrane Oxygenation (ECMO). High cost, unequal global access to ECMO centers, and complication rates present challenges to future ECMO expansion. Despite this, the available information supports the use of ECMO for H1N1-associated ARDS. Future studies and simulations should be conducted to expand the knowledge base on using ECMO as a treatment for pandemic influenza-associated ARDS, with particular attention on bridging gaps in access for the most vulnerable and affected populations.

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LIST OF ABBREVIATIONS

ANZ-ECMO ..... Australia and New Zealand Extracorporeal Membrane Oxygenation

ARDS ..... Acute Respiratory Distress Syndrome

av-ECMO ..... arterial-venous Extracorporeal Membrane Oxygenation

BSI ..... Bloodstream Infection

CESAR ..... Conventional Ventilator Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure

ECLS ..... Extracorporeal Life Support

ECMO ..... Extracorporeal Membrane Oxygenation

ELSO ..... Extracorporeal Life Support Organization

FRC ..... venous-venous Extracorporeal Membrane Oxygenation

HA ..... Hemagglutinin

HAI ..... Hospital Acquired Infection

ICU ..... Intensive Care Unit

NA ..... Neuraminidase

PEEP ..... Functional Residual Capacity

P_{inf} ..... Inflection Point

P_{IP} ..... Intrapleural Pressure

va-ECMO ..... venous-arterial Extracorporeal Membrane Oxygenation

VILI ..... Ventilation Induced Lung Injury

V_T ..... Tidal Volume

VQ ..... Ventilation-Perfusion

vv-ECMO..... venous-venous Extracorporeal Membrane Oxygenation

WHO..... World Health Organization

INTRODUCTION

In the spring of 2009, reports of a deadly "swine" flu were growing rapidly in Mexico and the United States ("CDC Novel H1N1 Flu | The 2009 H1N1 Pandemic," n.d.). Within months, this virus had spread to almost every country in the world and had infected hundreds of millions of people. This virus was found to be a novel strain of influenza A (H1N1). An infection is considered a pandemic when there is simultaneous transmission taking place worldwide, specifically out-of-season transmission for an influenza pandemic ("WHO | The classical definition of a pandemic is not elusive," n.d.). The 2009 H1N1 flu pandemic became one of the most ominous threats to public health in the 21st century. This virus showed that despite crucial advancements in infectious disease control and public health preventions, the world remains susceptible to fast-moving, highly contagious viruses. The speed at which the 2009 "swine" flu pandemic spread globally was unprecedented (Al Hajjar & McIntosh, 2010). While it was not the deadliest pandemic, there is much to be learned from the physiological manifestations and treatments that occurred. It is estimated that of the 284,400 deaths, 201,200 were attributed to respiratory causes including acute respiratory distress syndrome (ARDS) ("CDC Novel H1N1 Flu | The 2009 H1N1 Pandemic," n.d.). The threat for future respiratory-related pandemics remains high and it is important to research the use and efficacy of treatments such as extracorporeal membrane oxygenation (ECMO) during the 2009 H1N1 pandemic to best prepare for future pandemics of this kind.

Influenza

Influenza has been present for centuries with larger pandemics such as the 1918 "Spanish" flu, the 1957 "Asian" flu, the 1968 "Hong Kong" flu, and the 2009 "swine" flu. Influenzas are contagious diseases which are spread through droplet transmission such as coughing or sneezing. Influenzas are characterized by segmented, negative-strand RNA genomes and can be classified by type (A, B, or C) and subtype of the surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA) (Bouvier & Palese, 2008). Type A is the most common and virulent among humans and has been the type responsible for all influenza pandemics. Hemagglutinin is a protein that regulates viral attachment to the host cell and neuraminidase is an enzyme that regulates release of the virus from the infected cell (Appendix: Figures - Figure 1). The 2009 "swine" flu pandemic was characterized as Type A, hemagglutinin subtype 1, and neuraminidase subtype 1. The 1918 "Spanish" flu was A(H1N1), the 1957 "Asian" flu was A(H2N2), and the 1968 "Hong Kong" flu was A(H3N2).

The different types of influenza are caused from reassortment, which is the exchange of viral RNA segments between influenza viruses and antigenic variation, which can be in forms of antigenic shift and/or antigenic drift (Steel & Lowen, 2014). Antigenic shift is a process in which whole genetic segments of the hemagglutinin protein, and sometimes the neuraminidase enzyme, are exchanged with novel, transmissible subtypes from animal sources. Antigenic shifts are the cause of pandemics among the human population (Chang, Southard, & Sullivan, 2010). Antigenic drift is a process in which point mutations occur at the hemagglutinin and/or neuraminidase

antibody binding sites, creating new strains and preventing the host antibodies from effectively binding and signaling the immune system of invasion (Chang et al., 2010). These processes allow the virus to evade the host's immune system. These reassortment processes occur instantaneously and create dramatic changes in a virus, allowing effective infection into human populations.

Seasonal Influenzas

Seasonal influenzas, which the globe has become accustomed to, present with similar symptoms each year: fever, chills, muscle pains, weakness, and respiratory ailments (Morens, Taubenberger, Harvey, & Memoli, 2010). Common retroviral therapies such as oseltamivir, zanamivir, and peramivir are used as treatments for the flu (CDC, 2017). The WHO estimates that the flu results in ~1 billion cases per year and between 300,000 and 500,000 deaths ("WHO | Influenza," n.d.). Vaccines are widely available to prevent seasonal flu, but it is challenging for scientists to estimate the exact genetic makeup of the strain each year. While most influenzas appear in temperate regions during winter months, the 2009 pandemic was unique in that it developed in the spring and lasted throughout the summer months (Chang et al., 2010). As seen in the 2009 H1N1 pandemic, it is possible and probable that mutations and reassortments can occur and take advantage of global susceptibility.

Pandemic 2009 H1N1 relation to 1918 "Spanish" Flu

The 1918-1919 influenza was quoted to be the "Mother of All Pandemics;" infecting over 1/3 of the global population and resulting in over 50 million deaths worldwide (Taubenberger & Morens, 2006). Researchers thought that the 1918 pandemic disappeared from human circulation when the 1957 H2N2 "Asian" flu did not show resemblance to the 1918 pandemic. In 1977, however, these strains reemerged and have been present since. Genes from H1N1, H2N2, and H3N2 viruses originating in the 1918 pandemic have been found in almost all influenzas to this day, including the 2009 H1N1 pandemic.

Similar to the 1918 pandemic, the 2009 H1N1 pandemic was considered to be a novel virus. The 1957 and 1968 pandemics both showed genetic descendants of the 1918 virus, but the 2009 H1N1 was more genetically complex. The 2009 virus showed triple reassortment, updating its genome through avian, swine, and eventually human influenza genes (Morens et al., 2010). While the 1957 and 1968 pandemics exhibited a U-shaped mortality curve, where mortality was highest among the young and the old, the 2009 virus did not follow this curve. Instead, the 2009 virus was similar to the 1918 virus in that it exhibited a W-shaped curve, where relatively young and healthy adults between the ages of 20-40 years were perishing at high rates (Appendix: Figures – Figure 2). It is hypothesized that older adults had lower attack rates in 2009 due to circulating H1N1 viruses throughout their lifetime and more exposure to seasonal influenzas, compared to the more naïve populations (Morens et al., 2010). Regardless of these potential

protections, the 2009 H1N1 virus resulted in over 284,400 deaths and was present in 214 countries and overseas territories ("CDC Novel H1N1 Flu | 2009 H1N1," n.d.).

2009 H1N1 Development

The virus began in Mexico and moved to the United States, with the first confirmed case of the novel 2009 H1N1 swine flu being identified on April 15, 2009 in a 10-year-old boy in California. This virus was composed of genes originating from four different influenza virus sources: North American swine influenza virus, North American avian influenza virus, human influenza virus, and Asian and European swine influenza virus. The complex genetic makeup of the 2009 H1N1 virus made it a challenging task for researchers to identify cases and track the source of transmission; it took nearly one month to conclude that 2009 H1N1 was transmitted human to human. During this period the 2009 H1N1 virus spread around the globe rapidly and on June 11, 2009 the World Health Organization (WHO) declared a global pandemic of the 2009 H1N1 influenza ("WHO | World now at the start of 2009 influenza pandemic," n.d.). By June 25, 2009, the CDC estimated that the United States alone had 1 million cases of 2009 H1N1 ("CDC Novel H1N1 Flu | The 2009 H1N1 Pandemic," n.d.), increasing to over 60.8 million by the end of the pandemic ("Past Pandemics | Pandemic Influenza (Flu) | CDC," 2018). Swine flu spread to almost every country in the world by the end of the pandemic.

2009 H1N1 Affected Populations

The 2009 influenza pandemic was unique in that it predominantly affected children and young adult populations as compared to seasonal influenzas. The median age of affected populations in Canada, the United States, Chile, Japan and the United Kingdom was 12-17 years old and only 5% of hospitalized patients in the USA from April to mid-June 2009 were over 65 years old (Girard, Tam, Assossou, & Kieny, 2010).

It is hypothesized that cytokine storm may have played a role in the burden of disease among younger patients, as one study found that levels of IL-1, IL-6, TNF-α, IL-8, MCP-1, MIP1-β, and IP-10 were expressed at extremely high levels in lung tissues of 50 fatal H1N1 cases in 2009 (Gao et al., 2013). A cytokine storm is an unbalanced cytokine response involving an aggressive pro-inflammatory response and inadequate control of the anti-inflammatory response, resulting in a hyper-activating immune system (Qiang Liu, Zhou, & Yang, 2016). Cytokine storms can lead to damage of vascular surfaces and result in edema, capillary leakage, organ failure, and death (Sivro, Stein, & McKinnon, 2011).As younger populations have stronger immune systems than older adults, the likelihood of a cytokine storm is higher. Additionally, the W-shaped mortality curve of the 2009 virus (Appendix: Figures – Figure 3) showed that relatively young and healthy adults were perishing at high rates. It is hypothesized that younger populations were more susceptible to the 2009 virus as they had not been exposed to as many influenza strains in their lifetime (Morens et al., 2010).

In addition to younger populations, pregnant women were among those overly burdened by H1N1. As compared to season influenzas, the larger, pandemic influenzas

have shown that pregnant women are disproportionately burdened by disease. Changes in immunosuppression and both cardiovascular and respiratory physiology during pregnancy contribute to the increased susceptibility to severe outcomes related to H1N1 seen in pregnant women (Satpathy, Lindsay, & Kawwass, 2009). In a study summarizing data from 788 pregnant women from 50 state and local health departments in the United States, it was found that although pregnant women make up only 1% of the population, they represented 5% of the 2009 H1N1 deaths (Siston et al., 2010). Underlying causes such as asthma were seen in 43.5% of the deaths and 25.6% of the ICU admissions (Siston et al., 2010). Additionally, nearly one-third of pregnant women with H1N1 were hospitalized, and most were due to respiratory distress (Satpathy et al., 2009).

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a form of acute life threatening respiratory failure in which there is acute onset of pulmonary edema of non-cardiogenic origin, which decreases the compliance of the lung and presents with bilateral parenchymal pulmonary infiltrates on chest radiograph and a PaO2/FiO2 ratio ≤200 mmHg (Fanelli et al., 2013). The main cause of ARDS is sepsis with other causes including pneumonia, aspiration, drugs, trauma, embolism, and burns ("ARDS | National Heart, Lung, and Blood Institute (NHLBI)," n.d.). During the 2009 pandemic, however, the WHO found that H1N1 was responsible for 17.3 – 56% of ARDS mortalities (Zhang et al., 2012). Additionally, among H1N1 patients, ARDS was the main cause of death (Zhang et al., 2012).

During the pandemic, respiratory causes posed the largest threat to life. Of the 284,400 estimated deaths attributed to both cardiovascular and respiratory causes, 201,200 (95% CI: 105,700 – 395,600) were due to respiratory causes alone (Dawood et al., 2012). Almost all of the deaths were in people younger than 65 years old and over half of the deaths occurred in southeast Asia and Africa. The most common respiratory pathophysiological manifestation of 2009 H1N1 was acute respiratory distress syndrome (ARDS). ARDS is diagnosed based on the following criteria: acute onset of bilateral alveolar infiltrates on chest radiograph, PaO_2/FiO_2 ratio $\leq$ 200 mmHg, and pulmonary artery occlusion pressure of 18 mmHg or no clinical evidence of left atrial hypertension (Tathagat, Mathew, & deBoisblanc, n.d.). The H1N1 virus causes increased inflammation of alveoli and subsequent hypoxemia, leading to pulmonary edema (Zhang et al., 2012). Given that researchers' models suggest overall deaths ranged from 151,700 – 575,400 deaths ("First Global Estimates of 2009 H1N1 Pandemic Mortality Released by CDC-Led Collaboration | Spotlights (Flu) | CDC," 2017), Dawood et al's estimate that 201,200 respiratory deaths occurred would suggest that almost half, but perhaps all, deaths were due to ARDS, providing an ominous déjà-vu from the deadly experience in 1918.

Young adults, pregnant women, and those with preexisting medical conditions were at the highest risk of ARDS from H1N1 and were the most likely to experience severe hypoxemia and death. Most cases of 2009 H1N1-related ARDS required intensive care unit (ICU) hospitalization (Tathagat et al., n.d.) and an overall mortality rate was found to be 58% in one retrospective study conducted in Germany (Töpfer et al., 2014). In this study, H1N1-associated ARDS was found to differ from non-H1N1-associated

ARDS in that those with 2009 H1N1 had substantially longer recovery times for pulmonary gas exchange, more frequent demand of extracorporeal lung support, and longer ICU stays (Töpfer et al., 2014).

Extracorporeal Membrane Oxygenation

Treatments for H1N1-caused ARDS range based on access to care and indications. Since its first successful use for respiratory failure in 1927, extracorporeal membrane oxygenation (ECMO) has become a salvage strategy for patients around the globe (Makdisi & Wang, 2015). ECMO is a process in which there is a modified heart-lung machine that drains blood from a major vein, pumps the blood through a membrane lung (oxygenator), exchanges heat, and returns O_2-rich, CO_2-poor blood back into a major artery as in VA-ECMO or a major vein in VV-ECMO (Ventetuolo & Muratore, 2014) (Appendix: Figures – Figure 4). The goal of ECMO is to reduce strain on the cardiopulmonary system and to deliver O_2 and remove CO_2 from blood while the patient is recovering. ECMO has been used as a treatment for ARDS as a result of Influenza A (H1N1) virus infection since the start of the pandemic and has been shown to be an effective form of treatment in some studies (Kutleša et al., 2014), (ANZ ECMO Investigators & Davies, 2009), (Courouble et al., 2011). As it currently stands, there are only 126 ECMO programs registered with the Extracorporeal Life Support Organization (ELSO) in the United States, each of which are able to run only two ECMO machines at a time (Delaney et al., 2010). As it is predicted that the world will likely be presented with a pandemic influenza in the near future that could affect between 12-30% of the global

population (Delaney et al., 2010), it is necessary to learn from the 2009 H1N1 pandemic and the use of ECMO as a treatment for ARDS. This calls for the further exploration and research of ECMO as a treatment for H1N1-associated ARDS.

SPECIFIC AIMS AND OBJECTIVES

The specific aims and objective of this thesis include a review of treatment options for H1N1-associated ARDS, with a specific emphasis on the use of ECMO. Discussion of minimization of adverse side-effects will be explored. Outcomes and the capacity to expand ECMO usage in future pandemics will be discussed.

SEARCH STRATEGIES

PubMed was utilized as the primary database. A broad search for “Extracorporeal Membrane Oxygenation” and “Acute Respiratory Distress Syndrome” were done separately, each yielding 9,070 and 21,729 articles respectively. Search terms were combined and limited to the English language, which yielded 1,125 articles, and limited again to show only articles published in the last 20 years, yielding 980 articles. The Mesh terms for Extracorporeal Membrane Oxygenation, Acute Respiratory Distress Syndrome and Influenza A Virus were combined and the same limitations were placed, yielding 66 articles with the following search term: ((("Extracorporeal Membrane Oxygenation"[Mesh]) AND "Influenza A Virus, H1N1 Subtype"[Mesh]) AND ("Respiratory Distress Syndrome, Adult"[Mesh]) AND ("1997/01/01"[PDat] : "3000/12/31"[PDat]) AND English[lang]). The abstracts were scanned for relevance and articles were read fully. Analysis of bibliographies from relevant works was conducted in the search for additional articles on similar topics. Again, PubMed was utilized in similar search fashions to find articles relating to influenza biology, non-ventilatory and ventilatory lung management strategies, cost-effectiveness, and future concerns.

H1N1-ASSOCIATED ARDS: CAUSAL PATHWAY

H1N1 Viral Attachment and Pro-Inflammatory Signaling

Humans are exposed to H1N1 via airborne droplets. When inhaled, droplets may settle on any of the respiratory mucosal epithelia. The neuraminidase protein on the H1N1 virus aids in the virus' ability to find the appropriate receptor to bind to within the respiratory tract. The H1N1 viral life cycle begins when the hemagglutinin (HA) protein binds to a sialic acid-containing receptor on the host cell surface. Season influenzas predominantly bind to an α-2,6 sialic acid receptor, meaning that there is a bond to galactose at the α-2,6 position. Unlike most seasonal influenzas, the 2009 H1N1 influenza showed preferential binding to the α-2,3 sialic acid receptors that are found predominantly in the lower respiratory tract. The α-2,6 receptors are found along the entire respiratory tract, while α-2,3 receptors are found mostly in the lower respiratory tract in distal bronchioles, type 2 pneumocytes, and alveolar macrophages (Cheng, To, Tse, Hung, & Yuen, 2012).

When bound and endocytosed, the virus is able to take over cell machinery and replicate quickly. In the process, H1N1 triggers increases in cytokines, chemokines, and pro-inflammatory markers. One study found that levels of IL-1, IL-6, tumor necrosis factor-α (TNF-α), IL-8, monocyte chemoattractant protein-1 (MIP-1), macrophage inflammatory protein 1-β (MIP1-β), and interferon inducible protein-10 (IP-10) were expressed at extremely high levels in lung tissues of 50 fatal H1N1 cases in 2009 (Gao et al., 2013) and other studies found that in addition to the mentioned cytokines and chemokines, IL-10 and IFN-γ were also elevated (Cheng et al., 2012), (K. Sun, Ye, Perez,

& Metzger, 2011), (Tu et al., 2010). IL-1, IL-6, IL-8, TNF-α, MCP-1, MIP1-β, IP-10, and IFN-γ are all related to proinflammatory responses in the innate immune system. IL-10, however, is an anti-inflammatory cytokine (Moore, Malefyt, Coffman, & O'Garra, 2001). This study found that 2009 H1N1 was able to induce an exacerbated local immune response and apoptosis in lung tissue of autopsied patients based on histological samples (Moore et al., 2001). Additionally, the researchers found that the pandemic H1N1 virus was able to replicate within lung tissue more effectively than seasonal influenzas.

In another study conducted on ferrets, researchers found that in comparison to seasonal influenzas, the pandemic H1N1 virus caused higher levels of inflammatory cytokines such as IL-6, TNF-α, and IFN-α (Kang, Song, Lee, Kim, & Seo, 2011). Levels of alveolar macrophages and lymphocytes were significantly higher in pandemic H1N1-infected ferrets in comparison to both seasonal influenza and control ferrets five days post-injection (Appendix: Figures – Figure 5), suggesting a stronger immune response. In similarity with other studies, Kang et. al. found that pandemic H1N1 was able to replicate in the trachea, bronchi, and bronchioles while the seasonal H1N1 virus replicated only in the nasal cavity (Kang et al., 2011), (Moore et al., 2001). This study concluded that pandemic H1N1's ability to invade the lungs and induce pro-inflammatory cytokines contributed to the increased pathologic signs in infected organisms.

Acute Respiratory Distress Syndrome Definition and Stages

Ashbaugh and colleges first defined ARDS in 1967 and the syndrome has since been redefined multiple times with the most recent being the 2012 Berlin definition. The Berlin definition is regarded to be the most up to date and most generalizable definition. Under this definition, ARDS is defined as having an onset period of 7 days after lung injury or worsening respiratory symptoms, bilateral opacities that are consistent with pulmonary edema on chest radiograph or chest CT, P_aO_2/F_iO_2 ratio of 201-300mmHg for mild ARDS, P_aO_2/F_iO_2 ratio of 101-200mmHg for moderate ARDS, and P_aO_2/F_iO_2 ratio of ≤100 mmHg for severe ARDS while on a minimum positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) of 5cm of H_2O (Thompson, Chambers, & Liu, 2017).

The characteristic histological finding of a patient with ARDS is diffuse alveolar damage (DAD), which varies by the specific phase of ARDS (Meduri, Eltorky, & Winer-Muram, 1995). Both histological and gross anatomical changes occur in each phase of ARDS and are summarized in Appendix: Tables - Table 1 and 2. There are three stages to the typical ARDS cycle: the exudative phase of edema and hemorrhage, the proliferative phase of organization and repair, and the fibrotic phase end-stage fibrosis (Meduri et al., 1995). The exudative phase is triggered by either direct or indirect injury such as sepsis, pneumonia, or viral infection such as H1N1. Activation of resident alveolar macrophages leads to the release of proinflammatory cytokines and chemokines (Thompson et al., 2017). This immune response triggers neutrophil and monocyte chemotaxis as well as diapedesis of neutrophils to move towards the site of the infection. The increased

hydrostatic pressure due to the increased blood supply, increased vasculature permeability, and hyper-permeable alveolar tissue leads to leakage of proteinaceous fluid into the interstitium and alveolar space (Hughes & Beasley, 2016). Loss of epithelial integrity, preferential binding by viruses like H1N1, and direct injury from repetitive opening and closing of lung units (atelectrauma) contribute to the inactivation of type I and type II pneumocytes, denudated basement membranes, and denatured surfactant (Luh & Chiang, 2007), (Thompson et al., 2017). Hyaline membranes made of proteins, fibrin, and debris will form in the spaces. In conjunction with neutrophil-mediated epithelial injury, these mechanisms lead to severely impaired gas exchange, alveolar collapse, and atelectasis (Thompson et al., 2017). Atelectasis, which is collapse of portions of the lung, can lead to ventilation-perfusion (VQ) mismatch and physiological shunting of blood from poorly-ventilated areas to well-ventilated areas (Thompson et al., 2017).

The proliferative phase of ARDS is the phase in which an attempt at restoring homeostasis occurs. Proliferation of fibroblasts and pneumocyte hyperplasia characterize this phase. The fibroblasts migrate to repair the broken alveolar and interstitial spaces and there is some epithelial cell regeneration (Thompson et al., 2017).

The last phase, the fibrotic phase, is characterized by fibrotic lung architecture, and possibility cyst formation. Differing host responses can lead to restoration of lung architecture or permanent fibrosis with fibroblasts in airways and alveolar spaces on histological examination and collagen deposition (Meduri et al., 1995). Increasing fibrosis leads to decreased compliance and increased recoil forces, which make the act of

breathing extremely difficult. Not all patients will progress into the fibrotic stage, but if they do, long term mechanical ventilation is usually needed (Thompson et al., 2017).

Patients will present with typical H1N1 symptoms such as fever, cough, chills, with additional respiratory complications such as refractory hypoxemia, tachypnea, or dyspnea (Homsi, Milojkovic, & Homsi, 2010). Mortality varies based on stage but researchers estimate mortality rates for mild, moderate, and severe ARDS of 27%, 32%, and 45%, respectively (Hughes & Beasley, 2016). H1N1, like many other viruses, is able to trigger the type of immune responses and processes that lead to ARDS. It has been shown that the preferential binding of H1N1 to the receptors in the lower lung can lead to ARDS and eventual loss of pulmonary function (Töpfer et al., 2014), (Cheng et al., 2012).

VENTILATORY TREATMENT STRATEGIES FOR LIFE-THREATENING H1N1 AND ACUTE RESPIRATORY DISTRESS SYNDROME

Mechanical ventilation is a critical treatment strategy for the survival of patients with severe ARDS. Multiple studies have shown, however; that the possibility for ventilation induced lung injury (VILI) cannot be overlooked (Lee & Slutsky, 2001), (Qi Liu, Guo, Shan, Lan, & Chen, 2018), (Parekh, Abrams, Brodie, & Yip, 2018). Proper tidal volumes (V_T), ventilation rates, and pressures are necessary for the survival of the patient.

Positive End-Expiratory Pressures (PEEP)

PEEP is a mechanism in which a ventilator is set to hold a minimum pressure within the airways at the end of expiration. This process helps to recruit lung units and can aid in recovery after VQ mismatch and shunting occurs. Many studies have been conducted to study the most beneficial PEEP levels. High PEEP levels and large tidal volumes can lead to sheer stress and pulmonary barotrauma via the repetitive opening and closing of ducts (Muscedere, Mullen, Gan, & Slutsky, 1994). In a study using a rat model researchers assessed VILI using no PEEP, PEEP levels below the inflection point (P_{inf}), and PEEP levels above the P_{inf} (Muscedere et al., 1994). The P_{inf} is the point within a pressure-volume curve where there is an abrupt increase in slope. Muscedere et. al. found that the group without PEEP showed VILI predominantly in the bronchioles. The group with PEEP levels below P_{inf} showed decreased compliance after ventilation.

Researches posit that this decrease in compliance may be due to neutrophilic destruction of surfactant via mechanical ventilation, decreased surfactant by collapsed alveoli, or irreversible inactivation of surfactant by compression of surfactant films by over 50% (Muscedere et al., 1994). The group with PEEP levels above P_{inf} also showed VILI, predominantly in the alveolar duct regions. Muscedere et. al. showed that changing the PEEP levels will change the site of possible VILI, but that PEEP levels above the P_{inf} were the most beneficial to survival in the rat model.

In a randomized control trial of 53 ARDS patients by Amato et al researchers found that low V_T and higher PEEP levels were associated with increases in 28-day mortality, success in weaning off of mechanical ventilation, and reduced risk of barotrauma associated with VILI (Amato et al., 1998). Conservative strategies included low PEEP values (enough to keep P_{aCO2} between 35-38mmHg) and V_T of 12ml/kg and the protective strategies included V_T <6 ml/kg and PEEP values 2cmH_2O above P_{inf}. Overall, it was found that the protective strategies resulted in better outcomes.

Studies by (Chiumello et al., 2010), (Turani et al., 2010), and (Briel et al., 2010) found that higher PEEP levels were associated with better outcomes in terms of functional residual capacity (FRC), lung compliance, and survival among patients with ARDS. Additionally, the studies by Chimello et al found that among the H1N1 ARDS population elevated PEEP levels were beneficial.

Recruitment strategies using PEEP have been experimented for their efficacy in ARDS patients. A recruitment maneuver is one in which an intentional transient increase in transpulmonary pressure is applied with the idea that this will open atelectatic alveoli

and improve VILI (Paolo Pelosi, Gama de Abreu, & Rocco, 2010). Researchers have found, however; that this may also contribute to VILI and impair cardiac output through a reduction in venous return as mean thoracic pressure increases (Lim et al., n.d.). (Matos et al., 2010) found that using a maximal recruitment strategy by increasing PEEP levels from the customary level of 5 cmH_2O up to 45 cmH_2O was associated with exacerbation of VILI in their population of severe ARDS patients.

While it seems that there is consensus that PEEP levels should be greater than the inflection point pressures, there was a general lack of studies conducted on the pandemic H1N1 ARDS population in terms of PEEP levels.

NON-VENTILATORY TREATMENT STRATEGIES FOR LIFE-THREATENING H1N1 AND ACUTE RESPIRATORY DISTRESS SYNDROME

Conservative Fluid Management

Understanding of Starling forces and the importance of proper fluid management in intensive care is imperative for survival of the patient. As hydrostatic pressure rises and oncotic pressure falls in ARDS patients, pulmonary edema worsens. Pulmonary edema increases the work associated with breathing by decreasing compliance, creates hypoxemia through intrapulmonary shunts as a result of alveolar edema, and can cause pulmonary arterial hypertension via hypoxemia and pulmonary vascular compression (Neamu & Martin, 2013). Fluid management techniques are used to mitigate these risks and complications.

There has been much research on the effects of positive and negative fluid balance in patients diagnosed with ARDS. Positive fluid balance is when fluid accumulation or intake is greater than fluid output. Negative fluid balance is when fluid output is greater than fluid accumulation or intake. As fluids increase within the body of an ARDS patient with compromised endothelial and alveolar integrity, pulmonary edema worsens and can eventually lead to cardiovascular strain (Neamu & Martin, 2013), (Roch, Guervilly, & Papazian, 2011). While negative fluid balance has been thought to improve pulmonary edema, it can also decrease venous return resulting in decreased cardiac output.

In a randomized control trial of 1,000 patients with acute lung injury, conservative and liberal fluid management strategies were compared over 7 days for 60-day mortality (The National Heart & Network, 2006). The conservative group experienced restricted fluid intake and increased urinary output, while the liberal group experienced increased fluid intake and decreased urinary outputs. Results showed that the conservative group had lower mean arterial pressure, stroke volume, and cardiac index. The conservative group also displayed better lung injury scores, oxygenation indexes, and PEEP, but increased creatinine and blood urea nitrogen values. Additionally, metabolic alkalosis and electrolyte imbalances occurred at a greater frequency in the conservative group compared to the liberal group. Researchers did not find a significant difference in 60-day mortality between the conservative and liberal fluid groups, which was the main outcome of the study. The researchers did, however; find significantly improved lung function, increased number of ICU-free days and organ-failure-free days, and decreased time spent on mechanical ventilation in the conservative fluid group as compared to the liberal fluid group (The National Heart & Network, 2006).

While this randomized control trial did not show significant decreases in 60-day mortality, a second review of the data found that net negative fluid balance on the 4th day was associated with an odds ratio of 0.50 (95% CI, 0.28 – 0.89; $p<0.001$) for hospital mortality, indicating that compared to the positive fluid balance, those with negative fluid balance on the 4th day had 50% decreased odds of hospital mortality (Rosenberg, Dechert, Park, & Barlett, 2009).

With the aim that creating a net negative fluid balance will decrease pulmonary edema in patients with severe hypoxemia, clinicians may administer furosemide and/or albumin (Napolitano, Park, Raghavendran, & Bartlett, 2010). In a randomized control trial of 40 patients with acute lung injury/acute respiratory distress syndrome, researchers compared the use of furosemide with albumin or furosemide with placebo for 72 hours (Martin et al., 2005). Compared to those in the furosemide with placebo group, those in the furosemide and albumin group had significantly better outcomes in terms of increased oxygenation, total serum protein, and net fluid loss. By the third day, the PaO_2/FiO_2 ratio increased by 49mmHg in the albumin group while the placebo group decreased by 13mmHg. Additionally, the albumin group had a net fluid loss of 5,480mL by the third day compared to 1,490mL in the placebo group (Martin et al., 2005). This study supports the research on the benefits of net fluid loss in ARDS patients, as the use of albumin will increase capillary/plasma oncotic pressure and help to draw fluid from the interstitial spaces of the lungs back into circulation, thus decreasing the severity of the patient's pulmonary edema.

Conservative fluid management has been associated with long term cognitive and psychiatric morbidities. Mikkelsen et al. conducted a study on 102 patients from the Acute Respiratory Distress Syndrome Clinical Trials Network Fluid and Catheter Treatment Trial. Researchers found that patients who were placed under conservative fluid management strategies while hospitalized were more likely to have cognitive impairments (Mikkelsen et al., 2012). Additionally, patients who experienced lower partial pressure of arterial oxygen during hospitalization were more likely to have

psychiatric impairment. While the researchers agree that more studies should be done on this association, it raises awareness of possible adverse side effects long term. Overall, however; there appears to be consensus among the literature that conservative fluid management strategies were effective in overall outcomes of ARDS patients.

Prone Positioning

The positioning of a patient, either supine or prone can affect oxygenation and overall outcomes in ARDS patients and may create a more uniform ventilation-perfusion distribution (Koulouras, Papathanakos, Papathanasiou, & Nakos, 2016). The concepts of superimposed pressures, gravity, and shape matching can be used to explain the improvements in oxygenation seen in the prone position.

Superimposed Pressures

Within the chest cavity, each lung lies in a cavity separate from the other lung. The lungs, covered by visceral pleura, and the chest cavity, covered by parietal pleura, are separated by the intrapleural space, which is filled with a few milliliters of intrapleural fluid. The chest wall is composed of the ribs, diaphragm, intercostal muscles, and accessory muscles. Upon inspiration, contraction of the external intercostal muscles and the diaphragm work together to expand the volume of the chest cavity. As the external intercostal muscles contract, they pull the lower ribs towards the upper ribs, expanding the rib cage in both lateral and anterior-posterior directions. As the diaphragm contracts in a downward motion, it increases the vertical dimensions of the thorax.

Although separate, the lung and the chest wall move as one unit during respiratory excursions due to cohesive forces between their pleural surfaces. The lattice arrangement of elastin and collagen fibers in the lung contribute to its elastic properties, which allow the lungs to expand with the chest wall.

Compared to atmospheric pressure, the intrapleural pressure, P_{IP}, is usually negative because the lung, which adheres to the chest wall, tends to recoil, pulls on the intrapleural fluid filled "space" and causes P_{IP} to fall. Larger lung volumes cause greater lung recoil forces and lower P_{IP}. The chest wall also has a compliant structure, but unlike the lungs, tends to spring outward.

In the supine position, there is increased pressure in the dorsal lung due to the position of the heart and major vasculature (P. Pelosi, Caironi, Taccone, & Brazzi, 2001). A "sponge lung" model is a frequently used model to understand the concept of prone positioning. Since ARDS patients present with lung edema, the edema homogeneously increases overall lung weight resulting in decreased gas exchange in dependent lung regions and compression atelectasis seen by CT (Koulouras et al., 2016). When put in the prone position, the effect of heart position is reduced and there is more available lung for recruitment (Henderson, Griesdale, Dominelli, & Ronco, 2014).

Gravity

In the supine position, the dorsal chest wall is on a hard surface and so the majority of ventilated areas are in the ventral lung as this is the area with the most room for expansion and least compressive force. Gravity creates a gradient in intrapleural

pressure and distending pressure, which causes a decrease in alveolar size moving from ventral to dorsal lung. Lung edema and superimposed pressures is worsened by the effect of gravity in the supine position and gravity in the supine position creates large variation in alveolar size. In the prone position, however; the more compliant ventral chest wall is on the hard surface. This results in the less compliant dorsal chest wall being utilized to alter the intrapleural pressure and expand the lung. Additionally, gravity reverses the superimposed pressures and moves the compressive force from dorsal to ventral lung but, as discussed previously, this area of lung is smaller in size due to the heart and other intrathoracic structures (Kallet, 2015). The overall effect of gravity in the prone position creates a more homogenous alveolar inflation distribution (Koulouras et al., 2016) (Kallet, 2015) (Appendix: Figures – Figure 6).

Shape Matching

There is a difference in shape between the chest wall and the lungs. The cylindrical shape of the chest wall creates more available space for expansion of the conical-shaped lungs in their upper regions, resulting in a relatively greater expansion of nondependent alveolar units when supine (Koulouras et al., 2016). When prone, although there is increased compression due to gravity and superimposed pressures, regional expansion due to shape matching helps counteract these factors (Luciano Gattinoni, Taccone, Carlesso, & Marini, 2013).

In the supine position, superimposed pressures, gravity, and shape matching all act in the same direction towards lesser expansion of dependent alveolar units. In the

prone position, shape matching counterbalances these factors and overall there is a more homogenous inflation of dependent lung units (Luciano Gattinoni et al., 2013) (Appendix: Figures – Figure 7). In ARDS, pulmonary blood flow is relatively homogenous with slight preference for distribution to the dorsal lung regions, which improves the overall ventilation-perfusion ratio and oxygenation levels (Koulouras et al., 2016) (Kallet, 2015).

In a randomized control trial of 466 patients diagnosed with severe ARDS (PROSEVA Trial), researchers compared prone positioning of 16 hours to supine positioning to assess 28- and 90-day mortality (Guérin et al., 2013). Among the patients, 28 (6%) ARDS cases were due to influenza A (H1N1). Pa_{O2}/Fi_{O2} ratios were higher among those in prone positioning at the third and fifth days of ICU hospitalization. Twenty-eight day and 90-day mortality was significantly lower among those in the prone position than supine (Appendix: Figure – Figure 8), and the rate of successful intubation was significantly higher. This study, however; included the practice of turning the patient from prone to supine and back to prone at least once a day. Thus it is difficult to attribute the results solely to prone positioning and hence, more research on the potential benefit of repositioning is required (Guérin et al., 2013).

A case report on a 41-year-old male in an Italian ICU diagnosed with H1N1-associated ARDS highlighted the use of prone positioning when ECMO machines are unavailable (Gristina et al., 2010). The patient was exposed to prolonged prone positioning for 15 days and significant improvements were noted. This patient was originally being treated with enteral Oseltamivir, an anti-viral, but experienced difficulty

in intake and absorption of the drug in the prone position. The patient was subsequently switched to intravenous Zanamivir to eliminate the problem of position in drug intake. This case report highlighted the life-saving ability of prone positioning when ECMO machines are unavailable, but also discussed some potential complications that need to be taken into account such as the ability of the patient to receive and absorb medications when prone (Gristina et al., 2010).

The vast majority of studies on prone positioning for ARDS support the use in patients early on and with skilled nursing staff (De Jong et al., 2013), (Guérin et al., 2013), (Agrawal & Goel, 2015), (Davis et al., 2007), (Luciano Gattinoni et al., 2013). Some studies, however, found that although prone positioning did increase oxygenation, it did not affect overall mortality rates (L. Gattinoni et al., 2001), (Taccone et al., 2009).

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Extra corporeal membrane oxygenation is a complex form of extracorporeal technology that utilizes a modified heart-lung machine to provide respiratory and/or circulatory support to the most critically ill of patients. This technology allows for gas exchange outside of the body and was shown to be a positive rescue strategy for ARDS patients during the 2009 H1N1 pandemic (ANZ ECMO Investigators & Davies, 2009), (Delaney et al., 2010), (Zangrillo et al., 2013), (Turner et al., 2011), (Noah et al., 2011) (Rawal, Kumar, Yadav, & Sujana, 2017), (Kutleša et al., 2014).

History

Mortality from ARDS is between 34-58% (Peek et al., 2009) and those who survive their illness are often left with disabilities, both physical and emotional. As previously discussed, there are many downfalls of conventional ventilatory management such as volutrauma and other forms of ventilator induced lung injury. The idea of reducing ventilator settings to allow the lungs to rest while oxygenation is improved using an artificial membrane is appealing in light of these risks.

The principles applied in extracorporeal membrane oxygenation can be traced back to 1944 when Kolff and Berk discovered that blood became oxygenated as it passed through a cellophane chamber within an artificial kidney (Kolff et al., 1997). Since then, massive advances have been made in the field of extracorporeal life support (ECLS). Early studies, however; failed to show significant evidence that would support the use of such an invasive and costly treatment strategy (Morris et al., 1994), (Zapol et al., 1979). The Conventional Ventilator Support vs Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial, which was conducted on 180 individuals in the UK, led to the expansion of ECMO usage (Peek et al., 2009). This trial found that among those placed on ECMO, 6-month survival without disability was 63% compared to 47% in the conventional management cohort (Peek et al., 2009). This, combined with the widespread discussions of VILI, led to the expansion of ECMO globally.

ECMO was used as a treatment strategy for neonatal and pediatric traumas, cardiovascular stress, and bridge to transplant with some criticism until the outbreak of

pandemic influenza A H1N1 in 2009 when its use amplified dramatically (Mosier et al., 2015). Refractory hypoxemia from ARDS during the pandemic was frequently treated with ECMO yielding differing results but an overwhelmingly positive scientific opinion (Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators et al., 2009), (Zangrillo et al., 2013), (Noah et al., 2011), (Kutleša et al., 2014).

Types of ECMO set-ups

Extracorporeal membrane oxygenation has three set-ups: veno-arterial ECMO (va-ECMO), veno-venous ECMO (VV-ECMO), and arterio-venous ECMO (av-ECMO). There are different indications for each set up as will be discussed below. A typical ECMO circuit includes drainage cannulas, a blood pump, a membrane oxygenator, a heat exchanger, and tubing (Ventetuolo & Muratore, 2014).

Veno-Arterial ECMO (va-ECMO)

Veno-arterial ECMO provides both hemodynamic and respiratory support through the pumping of blood from the venous to arterial side. Blood is drained from a cannula inserted in either the inferior vena cava or right atrium, passes through the oxygenator and heat exchanger, and is returned through a cannula into either the ascending aorta (central ECMO) or femoral artery (peripheral ECMO) (Romano, Mendes, Park, & Costa, 2017). In this circuit (Appendix: Figures – Figure 9), blood bypasses both the heart and lungs as the circuit is in parallel with these organs.

va-ECMO reduces cardiac work and oxygen consumption while at the same time returning oxygenated blood to the systemic circulation. As this circuit is in parallel with the heart and lungs, it is only minimally decreasing blood flow through these organs and thus the final arterial oxygen content will be a mix of the less O_2 saturated blood from the impaired lungs and the more highly O_2 saturated blood from the ECMO set up (Romano et al., 2017). Decisions to use peripheral or central va-ECMO set ups should take into account the possibility of poorly oxygenated blood circulating in areas further away from the return of ECMO-oxygenated blood.

Arterio-Venous ECMO (av-ECMO)

Arterio-venous ECMO uses the patient's own arterial pressure to force blood through the gas exchanger and therefore from the arterial to the venous side. Patients in av-ECMO must have better cardiac function than those under va-ECMO (Martinez & Vuylsteke, 2012). The blood is drained from the femoral artery and is returned into the femoral vein. There is no pump in this circuit as the driving force is the patient's own arterial pressure (Appendix: Figures – Figure 10). This circuit, therefore, does not play as large of a role in oxygenation as the other forms of ECMO set ups. This circuit's primary goal is to remove CO_2, since oxygenated blood is passing from femoral artery to femoral vein (Martinez & Vuylsteke, 2012). While this is a relatively simple form of ECMO set up, it does not provide cardiovascular support and provides slightly less respiratory support than other forms and therefore, should be used in less-severe patients (Ventetuolo & Muratore, 2014), (Martinez & Vuylsteke, 2012).

Veno-Venous ECMO (vv-ECMO)

Veno-venous ECMO, like av-ECMO, does not provide hemodynamic support. This circuit removes blood from the venous side and pumps it back into the venous side (Appendix: Figures – Figure 11), aiding gas exchange by providing oxygenation while the lungs are able to rest (Martinez & Vuylsteke, 2012). Additionally, vv-ECMO is able to reduce the complications from VILI as it works outside of the body. This circuit, unlike va-ECMO, is in series with both the heart and lungs. Unlike va-ECMO, the blood will continue to pass through the lungs and heart and so it is necessary that the lungs have an adequate level of functioning (Martinez & Vuylsteke, 2012). Additionally, vv-ECMO has lower risks of thromboembolisms compared to va-ECMO (Martinez & Vuylsteke, 2012). vv-ECMO is the most widely used for ARDS patients.

ECMO Complications

The main complications during ECMO treatment are hemorrhage, infection, and neurologic impairments such as stroke.

Hemorrhage

Hemorrhage poses a significant risk during ECMO treatment. The large non-biologic ECMO surface results in thrombotic and inflammatory responses that can lead to embolisms (Martinez & Vuylsteke, 2012), (Ventetuolo & Muratore, 2014). Fibrinolytic responses also occur and can result in clotting factor deficiencies (Martinez & Vuylsteke, 2012). To mitigate these risks, the tubing in ECMO circuits is lined with heparin, an

anticoagulant, and patients are usually given anticoagulants intravenously. In a retrospective cohort study of 36 patients, of which 9 were positive for influenza A H1N1, researchers studied 14 patients in a severe hemorrhage group and 22 patients in mild hemorrhage group on vv-ECMO (Kreyer et al., 2017). Severe hemorrhage was defined as having any intracranial or intraabdominal bleeding, hemorrhage time of 50% while on vv-ECMO (meaning patient was hemorrhaging ≥ 50% of the time), needing 2 packed red blood cells (RBCs) per day or needing 6 packed RBCs in one transfusion (Kreyer et al., 2017). The severe hemorrhage group had significantly lower survival rates compared to mild hemorrhage groups while on vv-ECMO (43% vs. 91%; p=0.002) (Kreyer et al., 2017). This study also reported that hemorrhage complications are attributed to the death of up to 17% of patients on ECMO, highlighting the need for continued research on hemorrhage complications and ways to improve the ECMO circuits.

Infections

In an article by Biffi et al, researchers reported on the incidence and prevalence rates of hospital acquired infections (HAIs) and bloodstream infections (BSIs) during ECMO treatment (Biffi et al., 2017). ELSO data shows a prevalence of 21% for infection rates among adult patients (Vogel, Lew, Kao, & Lally, 2011), (Bizzarro, Conrad, Kaufman, Rycus, & Extracorporeal Life Support Organization Task Force on Infections, Extracorporeal Membrane Oxygenation, 2011), but prevalence of HAIs ranged from 9% - 65% with an average of 32.67% among the literature reviewed by Biffi et al [(Burket,

Bartlett, Vander Hyde, & Chenoweth, 1999), (Hsu et al., 2009), (H.-Y. Sun et al., 2010), (Pieri et al., 2013) , (Schmidt et al., 2012), (Aubron et al., 2013)]. Prevalence rates of BSIs ranged from 3 to 18%, with an average of 13%. Since only prevalence can be deduced from ELSO data, researchers analyzed single-center studies for incidence. Among the data, they found that incidence rates of HAIs ranged from 11.92 to 75.46 cases per 1,000 ECMO-days with an average of 41.46, and BSIs ranged from 2.98 to 20.55 episodes per 1,000 ECMO-days with an average of 17.36. Steiner et al found a three-fold risk of death among patients with BSI during ECMO treatment as compared to those without BSI, highlighting important ECMO complication to work to limit and treat.

While the invasive nature of ECMO would naturally result in an increased risk of BSIs, the high incidence rates of HAIs presents an area of improvement within ECMO care. With a widely understood association between length of hospital stay and BSIs (Green et al., 2015), (Kaye et al., 2014), (Różańska, Wałaszek, Wolak, & Bulanda, 2016) combined with the fact that those on ECMO treatment are already more likely to have increased length of stay, effective infection prevention strategies should be in place.

Neurologic complications

Stroke has been a widely regarded complication for patients on ECMO. In a retrospective study on 23,951 patients receiving ECMO from 2001 – 2011, researchers found that neurologic complications including acute ischemic stroke, intracranial hemorrhage, and seizures occurred in 10.9% of the patients (2,604) (Nasr & Rabinstein,

2015). In comparison to patients that did not suffer any neurologic complications, these patients had higher rates of discharge to a long-term care facility, longer lengths of stay in the hospital, and higher mortality rates. Another study, conducted by Guttendorf et al. found that neurologic complications occurred in 60% of their sample of 212 patients on ECMO (Guttendorf, Boujoukos, Ren, Rosenzweig, & Hravnak, 2014). It is necessary that precautions be taken to prevent neurologic complications and that more research is conducted on the association between ECMO and neurologic deficits.

ECMO during 2009 Influenza A (H1N1) Pandemic

Prior to the 2009 swine flu pandemic, there was much discussion surrounding the proper indications of ECMO and both survival and complication rates for patients. As the H1N1 pandemic caused more cases of ARDS globally, there was a surge in ECMO use in patients for whom conventional ventilation techniques were ineffective. Extracorporeal Life Support Organization (ELSO) is a global consortium of health care institutions that support research and development in extracorporeal life support. ELSO supports the results of the CESAR trial, which found a 63% survival rate at 6 months in those receiving ECMO (Extracorporeal Life Support Organization (ELSO), 2013). ECMO usage is associated with significant complications and, as such, is currently reserved for the most severe of patients.

There are many case series, case reports, and meta-analyses that support the use

of ECMO for H1N1 ARDS (Delaney et al., 2010), (Zangrillo et al., 2013), (Turner et al., 2011), (Noah et al., 2011), (Rawal, Kumar, Yadav, & Sujana, 2017), (Kutleša et al., 2014). During the pandemic, promising results coming out of Australia and New Zealand spread globally. In total, Australia and New Zealand experienced 8 times the amount of cases of H1N1 compared to the United States (ANZ ECMO Investigators & Davies, 2009). Their hospitals were overburdened with flu patients and patients suffering from ARDS. The Australia and New Zealand Extracorporeal Membrane Oxygenation Influenza Investigator team (ANZ ECMO) studied 68 patients with 2009 influenza A(H1N1)–associated ARDS that were treated with ECMO in 15 intensive care units (ICUs) between June 1 and August 31, 2009. There were 133 patients with 2009 influenza A(H1N1)–associated ARDS that were treated with conventional ventilation and were not referred for ECMO. While the P_aO_2/F_iO_2 ratio for severe ARDS is ≤100 mmHg while on a minimum PEEP or CPAP of 5 cmH_2O, the mean P_aO_2/F_iO_2 ratio among the 68 patients was 56 (range: 48 - 63) with a PEEP of 18 cmH_2O (ANZ ECMO Investigators & Davies, 2009). Additionally, the average age was 34.4 (range: 26.6 - 43.1) years. These data show the severity of respiratory compromise and the relatively young age among the patients selected for ECMO. The average duration of ECMO support was 10 days, and the cohort accumulated 828 days on ECMO in total (ANZ ECMO Investigators & Davies, 2009). While mortality rates on ECMO have been reported to range from 30-48%, the mortality rate among the patients in this study was only 21%, likely playing a role in the widespread use of ECMO during the H1N1 pandemic (ANZ ECMO Investigators & Davies, 2009).

A meta-analysis of 8 studies by Zangrillo et al. included 266 H1N1 ARDS patients treated with ECMO (Zangrillo et al., 2013). Similar to the ANZ-ECMO data, the median length of ECMO treatment was 10 days and patients had received mechanical ventilation for an average of 2 days prior to ECMO (Zangrillo et al., 2013). Mortality rates varied significantly among the studies, with Holzgraefe et al. reporting 8% (Holzgraefe et al., 2010), Patroniti et al. reporting 32% (Patroniti et al., 2011), and Chenaitia et al. reporting 65% mortality (Chenaitia et al., 2011). Zangrillo et al. used pooled estimates to calculate their reported estimate of 28% mortality among the 266 patients on ECMO (Zangrillo et al., 2013).

Noah et al. conducted a cohort study using data partly from the Swine Flu Triage study and analyzed data from 1 of the 4 ECMO centers in the United Kingdom during the pandemic (Noah et al., 2011). Individuals with H1N1-related ARDS who were being treated with ECMO were matched with non-ECMO individuals to study survival to hospital discharge. Researchers used 3 different matching techniques in order to account for differences in demographic, physiologic, or comorbidity factors including age, extent of hypoxemia, organ dysfunction, pregnancy, obesity, and use of ventilator settings. Among the 59 pairs of ECMO-referred and non-ECMO-referred patients, the relative risk of hospital mortality was 0.45 with a 95% confidence interval of 0.26-0.79 and a p-value of 0.006, indicating a statistically significant result (Noah et al., 2011). The hospital mortality rate among those referred for ECMO was 23.7%, representing a 55% decreased risk of hospital mortality in comparison to the non-ECMO-referred patients' mortality rate of 52.5% (Noah et al., 2011). This data is especially interesting as the study utilized

matching, allowing for better comparisons between groups but should be interpreted with some caution as there is no follow up data post-discharge.

Complications in these studies were not novel; stroke, hemolysis, and hemorrhage were the most frequently cited (ANZ ECMO Investigators & Davies, 2009), (Zangrillo et al., 2013), (Noah et al., 2011). While there are varying reported mortality rates from the pandemic, the overwhelming majority of studies support the use of ECMO for patients with H1N1-associated ARDS.

Future areas for concern

Access

ECMO treatments are conducted at ELSO-approved ECMO centers. ELSO reports that of the 160 ECMO centers registered in their system, 126 of the centers are in North America (Transonic, 2015). For areas of the world with higher H1N1 rates than the US such as New Zealand, Australia, and Southeast Asia, this poses potential problems for future pandemics. There is current research into mini, portable ECMO machines and potential attachments to dialysis machines that would allow them to function as ECMO, both of which appear promising for ECMO expansion (T. Müller et al., 2011).

Portable, compact ECMO machines

Müller et al. published a case report of a 30-year-old female who was successfully

treated with a compact and easily portable ECMO device (T. Müller et al., 2011). The patient experienced improved gas exchange and improved protective ventilation immediately after the start of ECMO, and after being weaned off of ECMO on the 12th day was successfully discharged after 21 days in the ICU (T. Müller et al., 2011). Authors cited the growing concern for the difficulty in transferring unstable patients to ECMO centers, especially in times of medical surge such as a pandemic of the nature seen in 2009, as the call to action for increased research and development of portable ECMO machines. In a later study of all H1N1-associated ARDS patients treated with ECMO in Porto, Portugal, researchers found that with the use of portable and compact ECMO machines they were able to have a survival to discharge rate of 60% (Roncon-Albuquerque et al., 2012). While their sample size was only 10 patients who were relatively young (mean of 40 years old), this data also supports the use of portable ECMO machines for H1N1-related ARDS.

Cost

ECMO is extremely expensive and resource-demanding. The CESAR trial found that the mean health care costs per patient were more than twice as high in patients who were referred for ECMO compared to patients who were treated with conventional techniques in the UK (Peek et al., 2009). This study also points out that while ECMO costs are relatively high, cost-effectiveness could be improved if there were decreased costs associated with ECMO transport.

Ratnani et al report that personnel resources, diagnostic and laboratory tests, radiology, ICU and operating room procedures, medications, and blood products all contribute to the high cost of ECMO (Ratnani, Tuazon, Zainab, & Uddin, 2018). In a systematic review by Harvey et al, researchers found that the average ECMO procedure cost $73,122 with the average patient having a total hospital cost of $210,142 (Harvey, Gaies, & Prosser, 2015). This may be an area in which portable, miniaturized ECMO machines would be of use.

In an observational study done on the miniaturized ECMO machines used in the Porto, Portugal study discussed above, researchers found that 17.6% of direct ICU costs were from ECMO-specific costs (Roncon-Albuquerque et al., 2014). Additionally, human resources represented the majority of the intensive care unit (ICU) costs from ECMO use, with a breakdown of other costs seen in (Appendix: Tables – Table 3). Mean cost per patient per day was 41,721 (€).

ECMO IN FUTURE PANDEMICS

Access, cost, complications, and training all play a role in the uncertainty of systems and surge capacity for the use of ECMO in future pandemics. The Center for Disease Control and Prevention as well as the World Health Organization routinely engage in planning exercises for future pandemics, knowing that they are inevitable. The 2009 H1N1 pandemic was an awakening; not because it was overly fatal, but because it spread around the globe so quickly. There is potential for future pandemics that move

quickly and are very lethal. The question of whether or not the world is ready to handle a pandemic similar in characteristics to the 1918 "mother of all pandemics" remains unanswered. Future pandemics, however; will likely continue to manifest in respiratory complications and more specifically, ARDS. The 2009 H1N1 experience with ARDS highlighted the need for continued research on treatment techniques.

Primary prevention, while the goal for global infectious disease management, will undoubtedly have weaknesses that influenza will take advantage of in growing to a pandemic level. Antigenic shift and antigenic drift continue to pose challenges for vaccine research and development, making the task of influenza prevention more difficult. Viral reassortment and potential for spillover of viruses from animal to human will create new strains of influenza, and the potential for strains to be genetically related to the 1918 pandemic remains high. The world is more globalized that ever before and transcontinental travel is at an all-time high. It is necessary to inform the public of ways to prevent influenza and treatments available if they do become ill. As primary prevention mechanisms fail in the context of an influenza pandemic, however; medical management becomes all the more important.

Non-ventilatory management strategies including conservative fluid management and prone positioning have shown uplifting results in the treatment of ARDS (Rosenberg et al., 2009), (Napolitano et al., 2010), (Patroniti et al., 2011), (Guérin et al., 2013) (Amato et al., 1998), (Chiumello et al., 2010). The 2009 experience showed the severity of the patient experience and the need for more intensive ventilatory management

techniques when conservative fluid management or prone positioning was not enough. Adequate PEEP levels continue to be important, but for the many patients who do not respond to ventilation management ECMO continues to be the rescue option. ECMO is complicated, costly, requires skilled specialists, and is not available in large numbers. Future research on miniature, portable machines and ways to improve the complication rates of ECMO is hopeful.

There is a general lack of information in the literature regarding systems capacity and medical surge in the context of ECMO use for ARDS during a pandemic. Undoubtedly, this will be of great importance in the future. The literature has strongly shown that ECMO is successful for the treatment of ARDS and that its application during the 2009 pandemic was life-saving to many. In the future, ECMO is promising for patients who have access to specialized treatment facilities. It is necessary that studies be conducted on preparedness and surge capacity using ECMO and that there be continued strides made towards decreasing ECMO complications.

CONCLUSION

The 2009 H1N1 pandemic affected millions and raised awareness about necessary interventions for acute pulmonary manifestations of the virus. Acute Respiratory Distress Syndrome resulted in loss of life worldwide and it is necessary to learn from this unfortunate result. Both non-ventilatory and ventilatory management strategies have proven to be effective in the treatment of early stage ARDS. Conservative fluid management and negative fluid balances were found to decrease strain and improve outcomes in ARDS patients (Neamu & Martin, 2013), (Roch et al., 2011), (Mikkelsen et al., 2012). The research supported prone positioning for both more homogenous ventilation/perfusion ratios and survival rates, but with some studies finding only benefit for oxygenation (Luciano Gattinoni et al., 2013), (Agrawal & Goel, 2015). Overall, however, the consensus seemed to support prone positioning for H1N1-associated ARDS (Gristina et al., 2010), (Guérin et al., 2013). Lower tidal volumes and higher PEEP levels were found to be the most beneficial combination for survival and reduced lung strain (Chiumello et al., 2010), (Turani et al., 2010), (Briel et al., 2010).

Due to the sheer number of patients and the virus' preferential aggravation of the lower lung, treatment options failed at times during the 2009 pandemic and invasive measures such as ECMO were relied upon. ECMO is an invasive, costly, resource-demanding intervention, but one that proved beneficial. In-hospital mortality rates among those referred for ECMO were significantly lower when compared to matched participants not referred for ECMO, with those referred experiencing a 55% decrease in-hospital mortality rate (Noah et al., 2011). Other articles echoed this success, with

mortality rates ranging from 8% to 65%, with a pooled estimate of 28% mortality (Zangrillo et al., 2013)(Holzgraefe et al., 2010), (Patroniti et al., 2011), (Chenaitia et al., 2011).

While complications on ECMO such as stroke, hemorrhage, and infection present important areas of concern, the threat of future pandemics makes systems capacity a crucial area for additional research. Expanded training programs should target the medical providers of the most vulnerable and affected populations, but high costs and feasibility issues may hinder progress. The future of medical device engineering, particularly in the field of miniature and portable ECMO machines, may bridge the gap in access to care by allowing for swift movement of resources to areas in need. Pandemic simulations and primary prevention strategies must continue, but as seen in 2009, pandemic influenza can and will evade these efforts. Medical providers should be well-trained to use all measures to manage ARDS on a global scale, including the use of potentially lifesaving extracorporeal membrane oxygenation.

APPENDIX: FIGURES

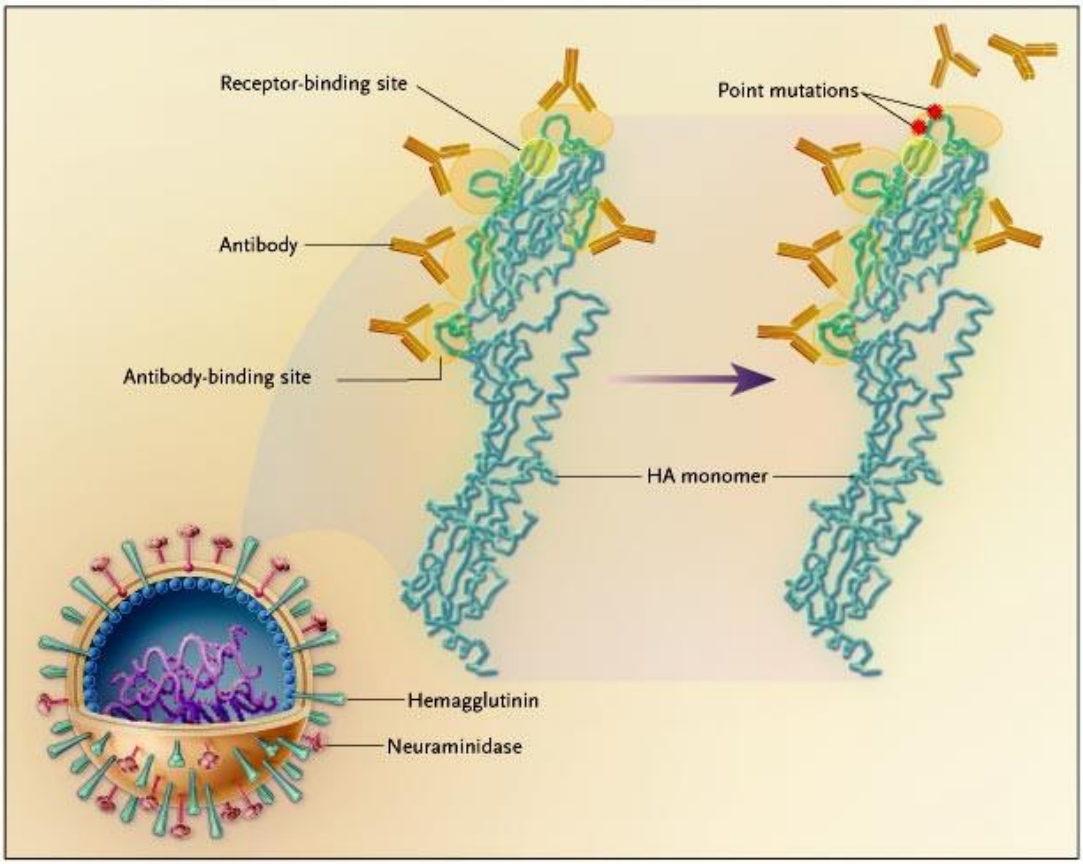


Figure 1: Structure of a Hemagglutinin Monomer and Location of the Five Known Antibody-Binding Sites in the HA1 Subunit. (Treanor, 2004)

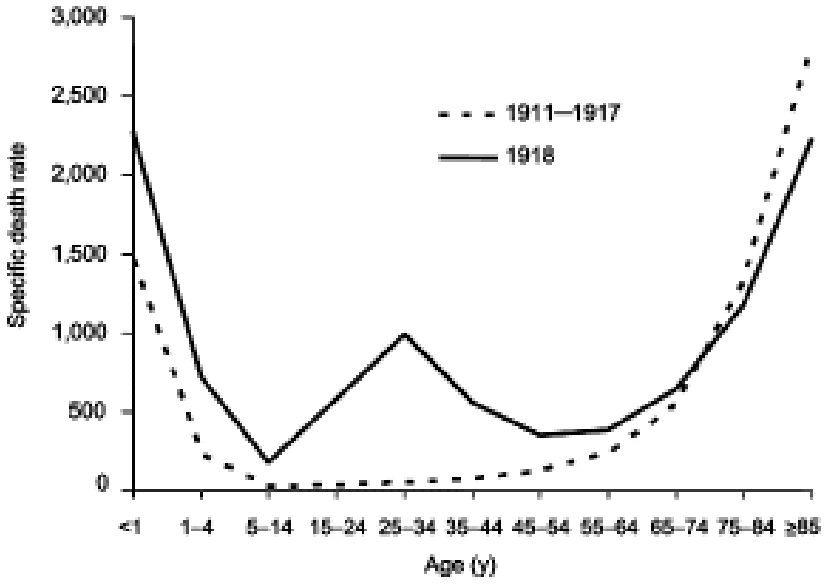


Figure 2: Mortality Curves: 1911 vs 1918 (Mitchell et al., 2010)

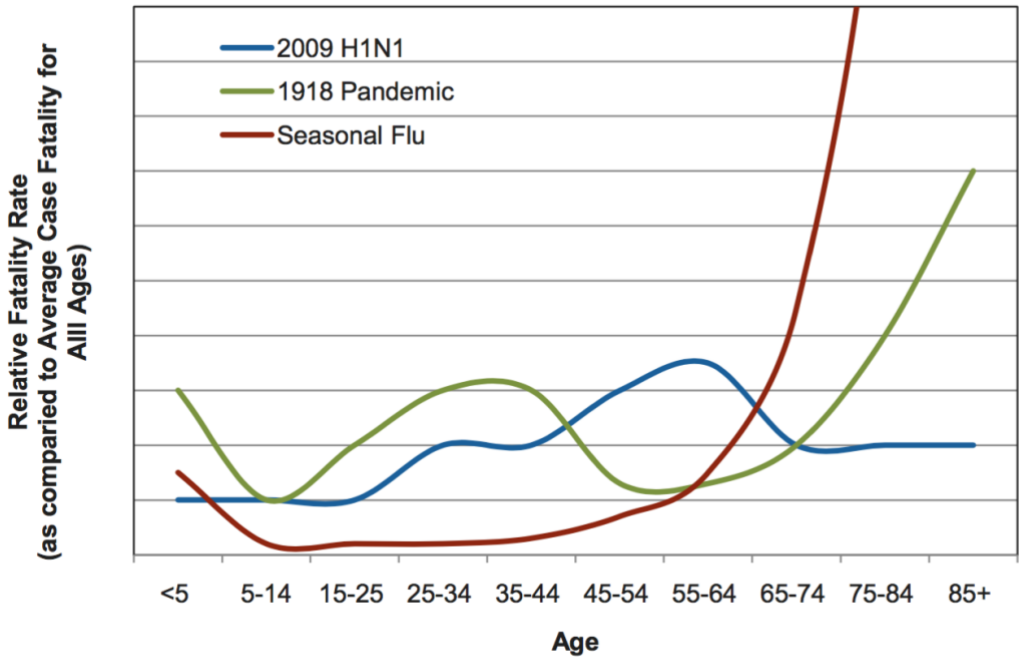


Figure 3: Age distribution of influenza mortality: comparing seasonal flu to the 1918 and 2009 pandemics

Figure 3: Mortality Curves: 2009, 1918, and Seasonal Flu (Chang et al., 2010)

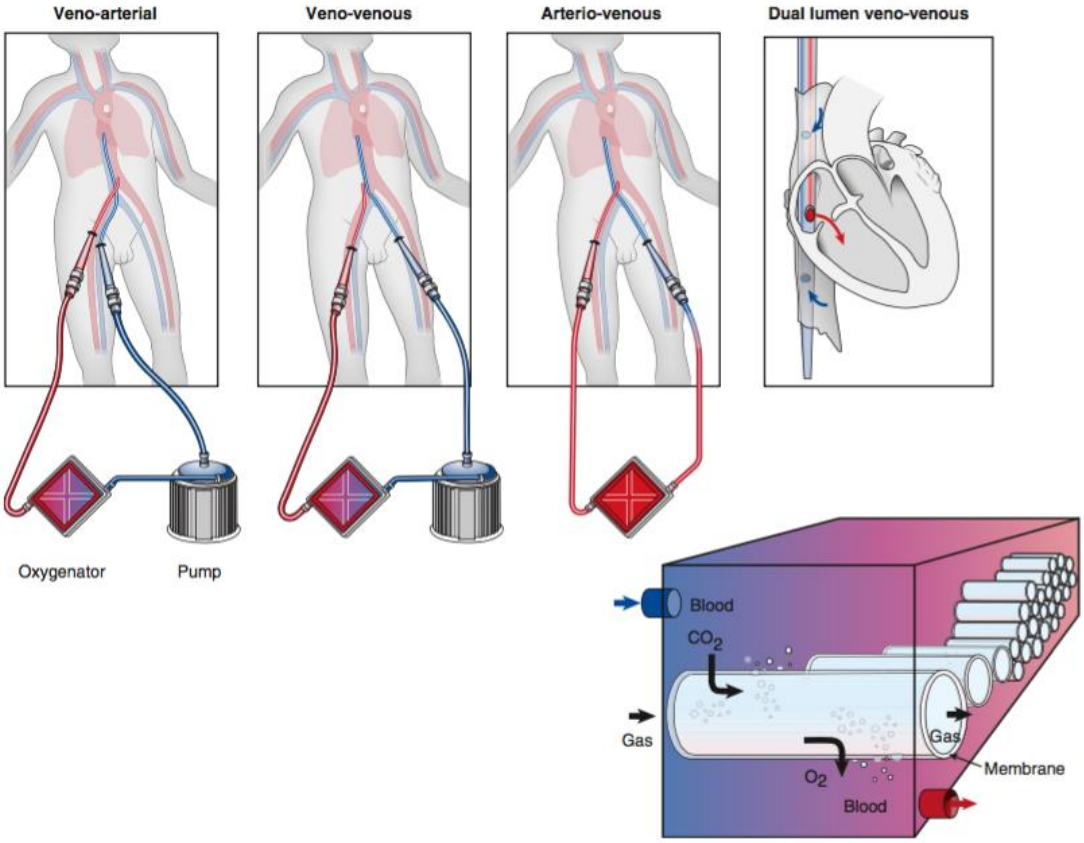


Figure 4: Three types of ECMO circuits (Ventetuolo & Muratore, 2014)

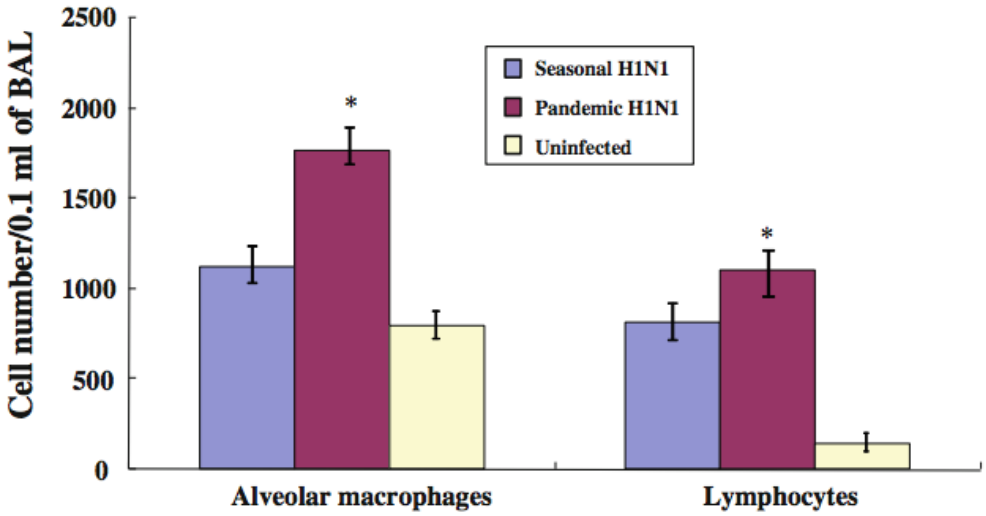


Figure 5: Levels of alveolar macrophages and lymphocytes during H1N1 events (Kang et al., 2011)

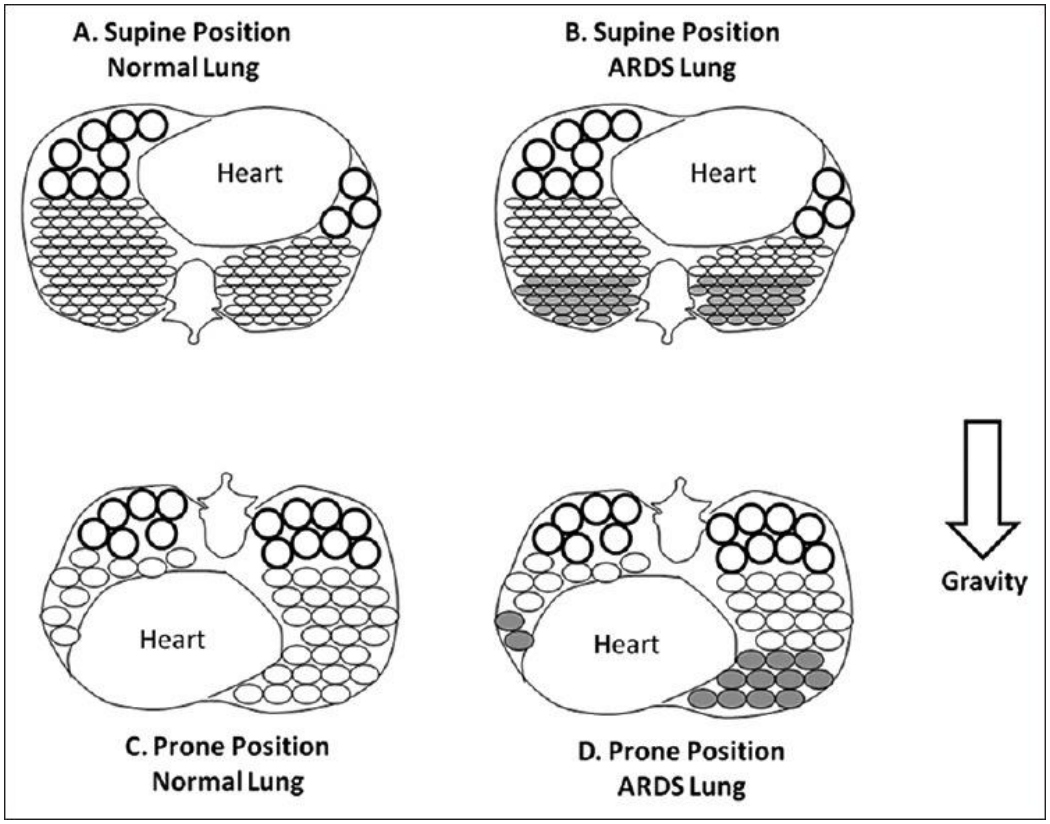


Figure 6: Effect of Prone Positioning (Agrawal & Goel, 2015)

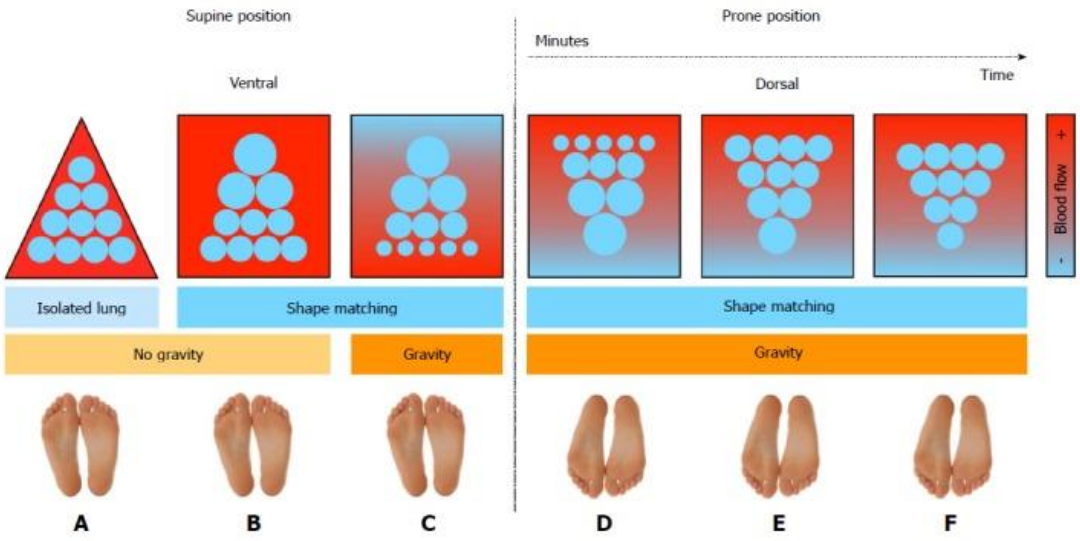


Figure 7: Effect of Gravity and Shape Matching on Prone Positioning (Koulouras et al., 2016)

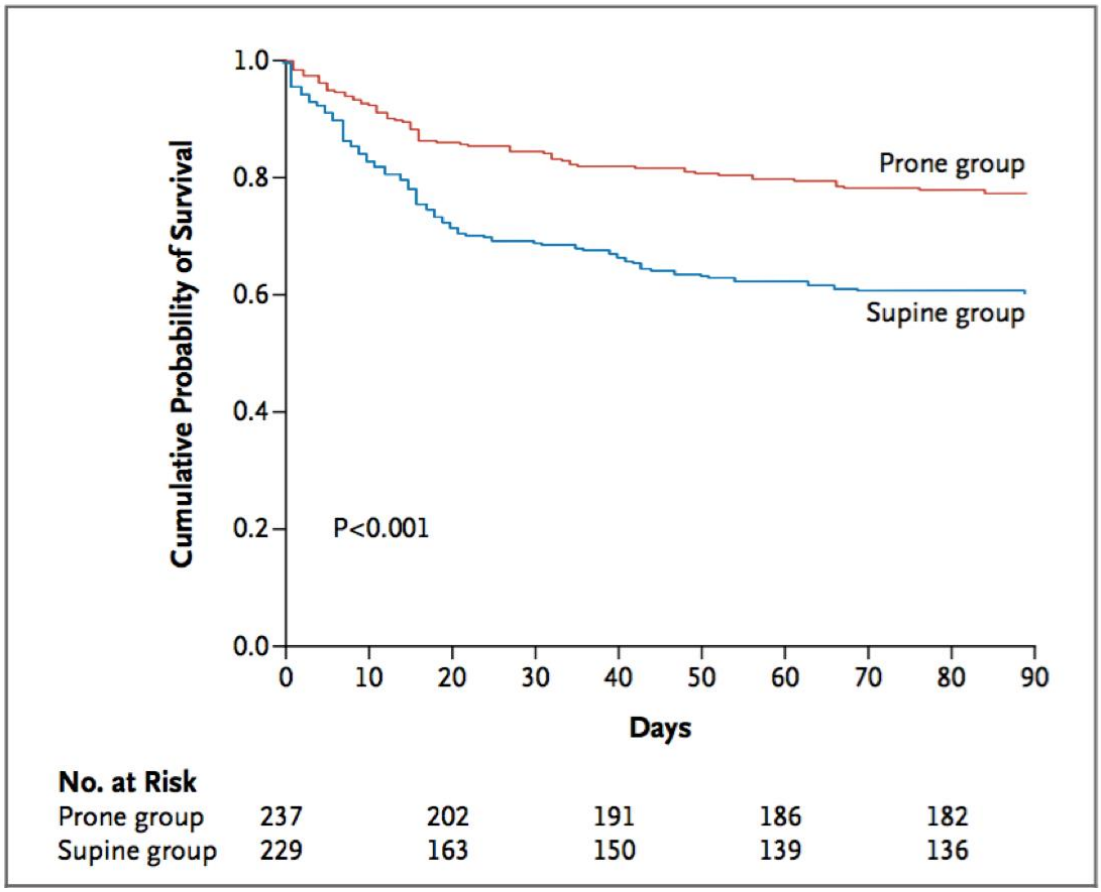


Figure 8: Kaplan-Meier Plot of the Probability of Survival from Randomization to Day 90 (Guérin et al., 2013)

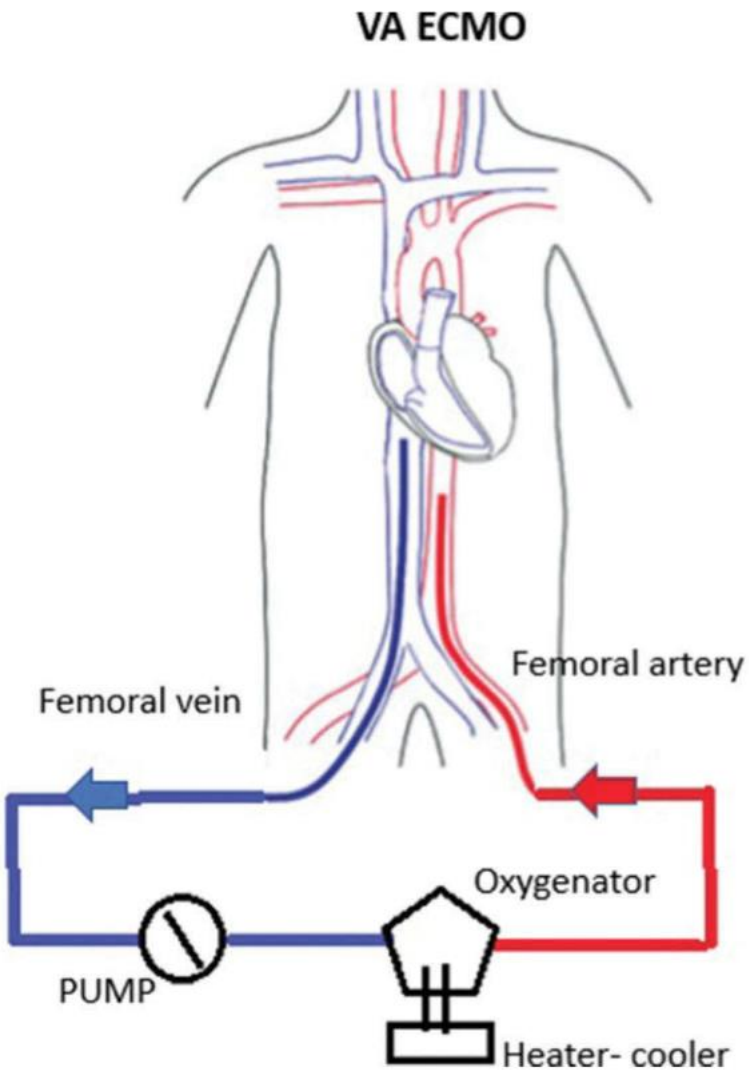


Figure 9: VA ECMO Circuit (Anand, Jayakumar, Aronow, & Chandy, 2016)

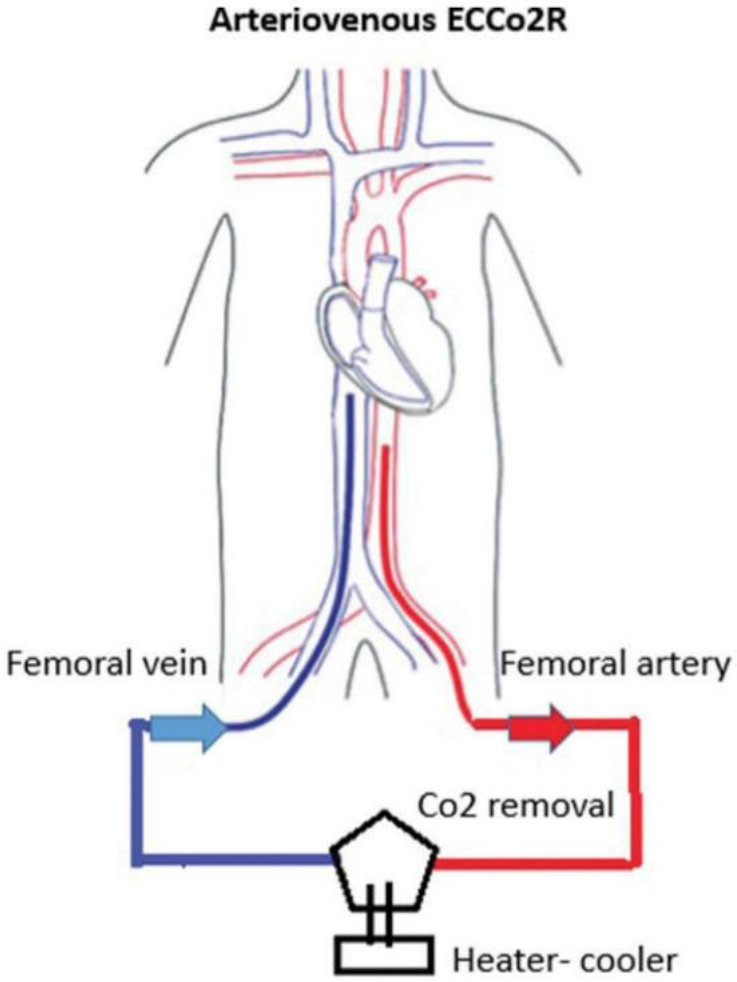


Figure 10: AV ECMO Circuit (Anand et al., 2016)

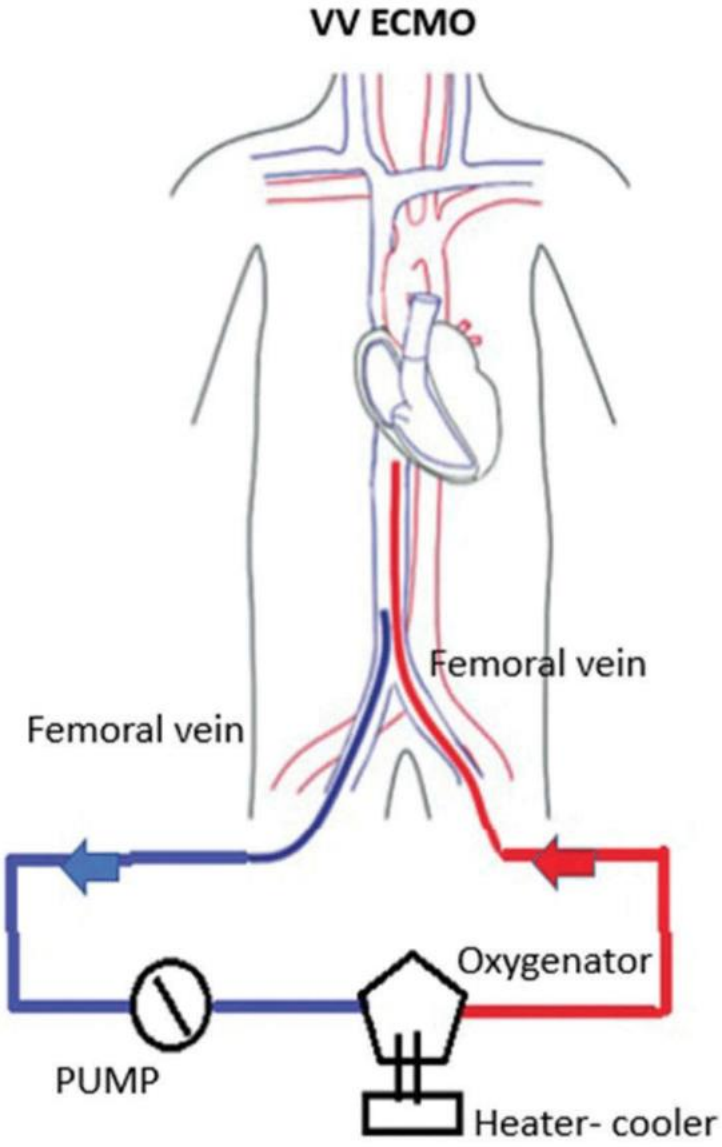


Figure 11: VV ECMO Circuit (Anand et al., 2016)

APPENDIX: TABLES

	Exudative	Proliferative	Fibrotic
Timing	Edema	Organization (repair)	Fibrosis
	Early (<1 week)	Intermediate	Late (3 weeks)
Macroscopic			
Consistence	Rigid, heavy	Firm, consolidated	Spongy, cystic
Appearance	Hemorrhagic	Pale gray	Pale
Microscopic			
Vasculature	Endothelial injury (mild)‡	Endothelial injury	Endothelial injury
	Congestion	Intimal fibroproliferation	Distortion
	Neutrophil aggregates	Medial hypertrophy	Compressed
	Minimal thrombi	Thrombi	Proliferation
Alveoli	Type I pneumocyte necrosis	Type 2 pneumocyte proliferation†	Fibrosis
	Inflammatory exudate	Myofibroblast invasion	Microcysts
	Hyaline membranes*	Increased fibronectin	
	Partial collapse	Collagen deposition	
Basement membrane	Denuded	Gaps with myofibroblast invasion	Disruption
Alveolar wall	Edema	Myofibroblast proliferation	Thick collagen
Alveolar duct	Dilated	Myofibroblast proliferation	Fibrosis
Interstitium	Volume‡	Volume‡	Volume+
	Edema	Myofibroblast proliferation	Fibrosis
Pleura	Subpleural ischemic changes	Subpleural necrosis	Subpleural necrosis

Table 1: Stages of ARDS (Meduri et al., 1995)

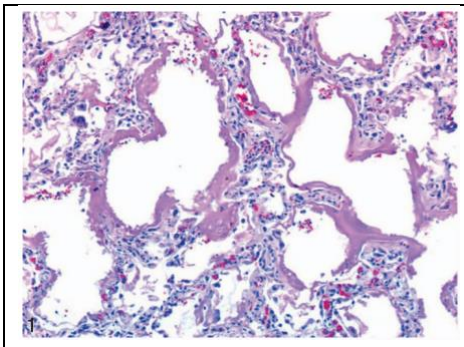
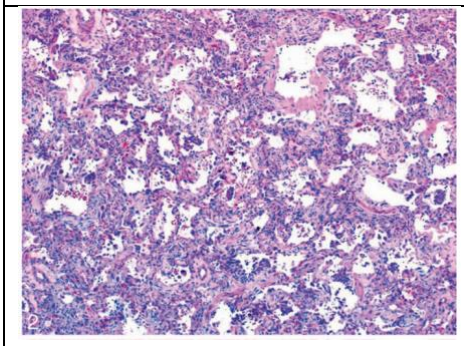
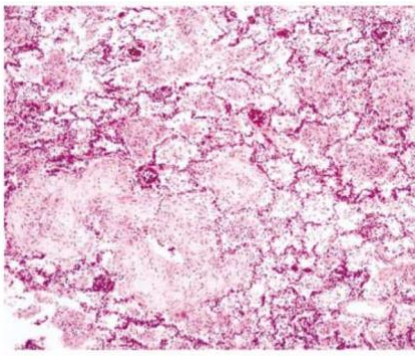
	Acute phase: Diffuse alveolar damage Prominent hyaline membranes line alveolar spaces Interstitium shows mild edematous widening (Hughes & Beasley, 2016)
	Proliferative phase: Diffuse alveolar damage Residual hyaline membrane in the upper right Interstitium shows prominent expansion by myxoid fibroblastic tissue Prominent type 2 pneumocyte hyperplasia (Hughes & Beasley, 2016)
	Granulation tissue in the distal air spaces with a chronic inflammatory-cell infiltrate (Ware & Matthay, 2000).

Table 2: Histological Findings in Stages of ARDS (Hughes & Beasley, 2016), (Ware & Matthay, 2000)

Cost drivers	Cost (€)/patient	Cost (€)/day	% ICU costs
Human resources	17,709 (13,288–23,638)	576 (548–577)	42.4 (36.9–46.2)
Disposable medical devices	10,789 (7,239–11,599)	286 (242–420)	25.3 (16.9–32.3)
Drugs	9,162 (5,808–10,512)	224 (203–338)	17.6 (15.7–22.2)
Laboratory and imagiology exams	5,565 (4,968–6,818)	155 (136–194)	11.4 (9.9–14.3)
Transfusions	109 (51–161)	2 (2–5)	0.17 (0.12–0.31)
Total	42,721 (33,358–56,801)	1,370 (1,250–1,439)	–

Costs are presented as median (interquartile range)

Table 3: Costs Associated with ECMO (Roncon-Albuquerque et al., 2014)

LIST OF JOURNAL ABBREVIATIONS

JAMA..... The Journal of the American Medical Association

NCBI..... The National Center for Biotechnology Information

PLOS..... The Public Library of Science

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