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The most common cause of death due to the H1N1 subtype of influenza A virus (swine flu) in the 2009 to 2010 epidemic was severe acute respiratory failure that persisted despite advanced mechanical ventilation strategies. Extracorporeal membrane oxygenation (ECMO) was used as a salvage therapy for patients refractory to traditional treatment. At Legacy Emanuel Hospital, Portland, Oregon, the epidemic resulted in a critical care staffing crisis. Among the 15 patients with H1N1 influenza A treated with ECMO, 4 patients received the therapy simultaneously. The role of ECMO in supporting patients with severe respiratory failure due to H1N1 influenza is described, followed by discussions of the nursing care challenges for each body system. Variations from standards of care, operational considerations regarding staff workload, institutional burden, and emotional wear and tear of the therapy on patients, patients’ family members, and the entire health care team are also addressed. Areas for improvement for providing care of the critically ill patient requiring ECMO are highlighted in the conclusion. (Critical Care Nurse. 2011;31[5]:e8-e24)

Despite marked advances in the treatment of severe acute respiratory distress syndrome (ARDS), a subset of patients with this diagnosis is refractory to even the most aggressive management strategies. In particular, patients infected with subtype H1N1 of influenza A virus were some of the most challenging patients with ARDS in many years. Throughout the spring and fall of 2009, the world experienced its first influenza pandemic since 1968. H1N1 was responsible for more than 17 700 deaths around the globe.1–3 The World Health Organization reported 59 million cases, 265 000 hospitalizations, and 12 000 deaths in the United States alone.3 Although most cases were acute and self-limited, nearly half of the patients hospitalized were less than 18 years old.4 In the United States and Canada, 9% to 31% of hospitalized patients were admitted to an intensive care unit (ICU), and the mortality rate was a staggering 14% to 46%.4–6 The most common cause of death was severe acute respiratory failure despite advanced mechanical ventilation strategies and the use of lung rescue therapies.4 In New Zealand and Australia, when even the most aggressive mechanical ventilation strategies and lung salvage efforts

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were unsuccessful, extracorporeal membrane oxygenation (ECMO) became a practical rescue therapy option and prompted the use of ECMO in the United States for patients with H1N1 influenza A who were refractory to treatment.9

Legacy Emanuel Hospital is a 396-bed community level I trauma center in Portland, Oregon. ECMO has been used at our center for 20 years for patients with severe respiratory and cardiovascular failure due to a variety of causes, but our expertise and resources were quickly challenged by the H1N1 epidemic. During this crisis, ECMO was initiated for 12 adults and 3 children at our hospital; the survival rate was 60%. The staff of our 14-bed adult ICU cared for the 12 adult patients. At the peak of the crisis, 4 patients were being treated with ECMO in our unit at the same time. Although many of our long-standing practices for ECMO therapy were validated during this time, we had countless opportunities to learn, improvise, and improve care.

In this article, we review our experience in using ECMO to support patients with severe respiratory failure due to H1N1 influenza and other causes, describe the challenges in nursing care and variation from standards of care that were necessary, and discuss operational considerations of staff workload, institutional burden, and emotional wear and tear of ECMO on patients, patients’ family members, and the entire health care team.

H1N1 Influenza A

The World Health Organization declared the first phase of the global H1N1 pandemic in June 2009.10 The highest illness rates were in children and young adults. The sparing of adults more than 60 years old was thought to be due to their previous exposure to similar influenza viruses earlier in their lives.11,12 Many patients hospitalized because of the illness had no preexisting conditions. Patients with underlying conditions associated with severe illness included pregnant women in their second or third trimesters, women less than 2 weeks postpartum, and patients with immunosuppression or neurological disorders.4,5,7 Severe or fatal cases were 5 to 15 times higher in patients with a body mass index greater than 40, making morbid obesity a contributing factor to poor outcome.7,8,11

A full review of clinical and management aspects of H1N1 is beyond the scope of this article. However, Table 1 gives clinical manifestations,4,5,8,10,14-17 and Table 2 gives medical interventions.1,2,8,12,15,18,19 For additional information, see the reviews of Kumar et al7 and the Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza.18 For many critically ill patients with H1N1 influenza A, the typical interventions of supportive care, antiviral agents, and lung-protective strategies were effective. For an unlucky

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few, more aggressive measures were required to address refractory pulmonary failure and evolving multiple organ dysfunction. The use of high-frequency oscillatory ventilation in conjunction with ECMO was recently shown to markedly improve oxygenation in patients with H1N1 influenza, although the effect on mortality was less clear. ECMO is currently considered a reasonable rescue therapy option when a patient’s condition continues to deteriorate despite traditional aggressive efforts to reverse life-threatening respiratory failure.

**Extracorporeal Membrane Oxygenation**

ECMO is mechanical cardiopulmonary support used to treat severe respiratory failure, cardiac failure, or both. Initially developed for use during cardiac surgery, ECMO can be applied in the operating room or in the ICU if prolonged therapy is needed. ECMO provides a salvage therapy that can be used in extreme cases of ARDS refractory to conventional ventilation techniques. ECMO is mechanical cardiopulmonary support used to treat severe respiratory failure, cardiac failure, or both. Initially developed for use during cardiac surgery, ECMO can be applied in the operating room or in the ICU if prolonged therapy is needed. ECMO provides a salvage therapy that can be used in extreme cases of ARDS refractory to conventional ventilation techniques.

## Table 1 Clinical manifestations of H1N1 influenza A

<table>
<thead>
<tr>
<th>Mild disease</th>
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<tbody>
<tr>
<td>Sore throat</td>
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<tr>
<td>Rhinorrhea</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Chills</td>
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<tr>
<td>Nausea, vomiting, diarrhea</td>
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<td>Muscle pain</td>
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<td>Malaise</td>
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<table>
<thead>
<tr>
<th>Severe disease</th>
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</thead>
<tbody>
<tr>
<td>Dyspnea, hypoxia, hemoptysis, purulent sputum</td>
</tr>
<tr>
<td>Respiratory failure within 4-5 days of initial signs and symptoms</td>
</tr>
<tr>
<td>Chest pain</td>
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<tr>
<td>Prolonged or recurrent fever</td>
</tr>
<tr>
<td>Altered level of consciousness</td>
</tr>
<tr>
<td>Hypotension and severe dehydration</td>
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<tr>
<td>Multisystem organ failure</td>
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<tr>
<td>Fulminant pneumonia</td>
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<tr>
<td>Diffuse pneumonitis</td>
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<tr>
<td>Diffuse alveolar drainage</td>
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<tr>
<td>Septal edema</td>
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<tr>
<td>Tracheitis</td>
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<tr>
<td>Necrotizing bronchiolitis</td>
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<td>Alveolar hemorrhage</td>
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## Table 2 Treatment of H1N1 influenza A

| Supportive care and management of signs and symptoms associated with influenza |
| Administration of neuraminidase inhibitors such as oseltamivir (Tamiflu) and zanamivir (Relenza) |
| Antibiotics to treat secondary sources of infection |
| Diuretics and continuous renal replacement therapy for oliguric renal failure |
| Immediate availability of neonatal intensive care unit equipment and personnel for pregnant patients with viable fetus |

| For rapid progression of respiratory failure |
| Early intubation within the first 24 hours of admission |
| Aggressive pulmonary salvage strategies |
| Low tidal volumes |
| Inverse inspiration-expiration ventilation |
| High-frequency percussive or oscillating ventilation |
| Deep sedation |
| Neuromuscular paralysis |
| Prone position |
| Inhaled nitric oxide |

| Extracorporeal membrane oxygenation |
is needed, ECMO can be configured as venoarterial or venovenous. With venoarterial ECMO, blood extraction is typically via the femoral vein, and blood return is to any central artery, usually the femoral artery with the cannula terminus in the iliac artery. With venovenous ECMO, both the heart and the lungs are rested. Cardiac output is determined by setting the mechanical pump to circulate a programmed volume in liters per minute of newly oxygenated blood. Venoarterial ECMO is used primarily to preserve both cardiovascular and pulmonary function.

Venoarterial ECMO provides pulmonary support only and functions as an artificial lung for patients with severe pulmonary failure. This method relies on the patient’s heart to circulate the newly oxygenated blood. Thus, the lungs can rest without being subjected to high oxygen concentrations or ventilation pressures that might exacerbate the underlying cause of the respiratory failure. In adults, venovenous ECMO can be used with either 2 single-lumen catheters or 1 double-lumen catheter. When 2 catheters are used, blood is extracted via a cannula placed in a large vein, usually the femoral vein, with the cannula terminus in the inferior vena cava. The blood is returned via another large vein, usually the jugular vein, and the cannula terminus is in the superior vena cava. With a single dual-lumen catheter, the venous drainage ports are situated in the inferior and superior vena cava; the return port rests in the right atrium and ideally is aimed directly at the tricuspid valve.

The essential components of a typical venovenous ECMO circuit include the console, access cannulas, tubing, pump, oxygenator, inline arterial and venous oxygen saturation sensors, heat exchanger, and a bridge (Figure 2). At Legacy Emanuel, the cannulas are placed by either a cardiothoracic surgeon or a trauma surgeon. Cannulas range in size from 8F to 16F outer diameter for single-lumen catheters and from 13F to 31F outer diameter.
for double-lumen catheters. The circuit consists of 0.95-cm (3/8-in) polyvinylchloride tubing lined with a biocompatible coating. Deoxygenated blood is carried from the venous drainage cannula through the tubing to the pump. The pump can be either a roller pump or a centrifugal pump that propels the blood forward to the oxygenator, also referred to as the membrane lung, where oxygen and carbon dioxide exchange occurs. Newly oxygenated blood moves from the oxygenator to the heat exchanger, which uses a temperature-regulated circulating water source to maintain normothermia. From the heat exchanger, the blood travels to the return port or cannula, where it is infused back into the patient’s native circulation.

In our unit, the circuit contains a “bridge” between the drainage and return cannulas. This short length of pressure tubing allows the ECMO specialist to maintain flow within the circuit when flow to the patient has been interrupted because of events such as planned cannulation or emergency displacement of a catheter.

The ECMO pump and circuit can be managed by licensed cardiovascular pulmonary perfusionists or by specifically trained bedside ICU nurses or respiratory therapists. Historically, with adult patients in our ICU, ECMO has been managed by a perfusionist. The primary responsibility of the specialist is to maintain optimal flow of the ECMO circuit, remaining ever vigilant to prevent adverse events. A myriad of circuit complications may occur during ECMO therapy, including recirculation; kinking of circuit tubing; clotting and clogging within the circuit; vessel perforation, vessel occlusion, and other vessel damage related to cannulation; and unplanned cannulation. Recirculation refers to the phenomenon by which a quantity of deoxygenated blood from the ECMO circuit returns directly back into the circuit via the venous drainage cannula. Recirculation occurs because of the proximity of the venous drainage cannula and the return cannula. Four factors affect the amount of recirculation: ECMO pump flow, position of the venous catheter, native cardiac output, and right atrial blood volume. The effects of recirculation can be minimized by ensuring proper cannula placement, maintaining optimal flow through the ECMO circuit, and optimizing the patient’s native cardiac output.

If a clot develops in the circuit or a cannula unexpectedly becomes dislodged, immediate intervention by the entire ECMO team is required. In these emergency situations, the focus of the bedside nurse is to provide supportive care to the patient while the specialist attends to the circuit. If a cannula is displaced, direct pressure is applied to the site of displacement while the ECMO specialist simultaneously unclamps the bridge to maintain flow through the circuit, and the surgical team prepares to reinsert a new cannula.

The ECMO specialist frequently assesses the circuit tubing and components for signs of kinking and clotting. Oxygen, blood gas, and pressure censors are monitored for adequate flow and volume status within the circuit. The procedures and monitoring activities of the ECMO specialist are extensively described by Rees and Waldvogel.

Nursing Priorities for ECMO Patients

At Legacy Emanuel Hospital, the ICU nurse is responsible for providing and coordinating the care of patients treated with ECMO. This responsibility includes monitoring each body system for clinical changes, anticipating complications related to ECMO, and supporting the patient’s family. These essential activities are described in the following sections and illustrated in the case study.

Neurological Considerations

In our ECMO patients, assessment and management of neurological status was of paramount importance. Patients were given sedatives and paralytic agents to minimize oxygen demand and prevent dislodgement of the cannulas. Sedation and analgesia with midazolam and fentanyl were often already established by the time ECMO therapy began. Propofol was not used because the perfusionists and physicians were concerned that its lipid base might occlude the ECMO circuit oxygenator. However, subsequent conversations with other ECMO centers have revealed that propofol can be used in ECMO without complication. Infusions for sedation and analgesia were titrated on the basis of physiological indicators of pain and anxiety (eg, tachycardia, hypertension, facial grimacing, patient movement). Our goal was to achieve the equivalent of a Riker score of 1, described as minimal or no response to noxious stimuli, does not communicate or follow commands. Upon cannulation, an infusion of the neuromuscular blocking agent cisatricurium was
started. A train-of-4 nerve stimulator was used hourly to titrate the paralytic agent to a goal of 2 of 4 twitches. Many of our patients required surprisingly high doses of sedatives and analgesics. Doses of midazolam as high as 10 to 15 mg/h and doses of fentanyl of 250 μg/h or greater were common. This requirement was thought to be a result of adhesion of the medications to either the ECMO circuit tubing or the oxygenator. Fentanyl can have an 86% adsorption rate in ECMO circuits with the same type of hollow fiber oxygenator as the one we used.27 We hypothesized that the same phenomenon was occurring with other continuous intravenous infusions despite the lack of definitive literature on this issue.

**CASE STUDY**

A 31-year-old Hispanic woman (EP) with a history of morbid obesity, type 2 diabetes mellitus, and hypertension was transferred from an outside hospital with suspected H1N1 infection complicated with severe pneumonia and acute respiratory distress syndrome. Six days before admission, EP was seen in the emergency department of the referring hospital after experiencing 5 days of flulike symptoms, shortness of breath, and fever.

The patient was admitted to the outside institution with oxygen saturations of 80% to 89% and a chest radiograph that showed bilateral infiltrates. She was treated with 100% oxygen via nonrebreather mask and given oseltamivir, vancomycin, piperacillin, and tazobactam. Her condition quickly deteriorated and she was intubated that night. Despite increasingly aggressive ventilator settings, EP’s respiratory status continued to decline, and an infusion of norepinephrine was started to maintain a perfusing blood pressure. Positive H1N1 status was confirmed on day 5 after admission.

The following day, EP’s physicians contacted our tertiary referral center for a consultation regarding extracorporeal membrane oxygenation (ECMO). The patient was deemed to be a candidate for treatment with ECMO. Later that day, the mobile surgical transport team was dispatched by ambulance to retrieve the patient. When the team arrived, they found the patient intubated and undergoing mechanical ventilation with an airway pressure release ventilation mode at a fraction of inspired oxygen (FiO2) of 1.0. She was hypotensive and had oxygen saturations from 80% to 83%. An arterial catheter, a urinary catheter, a nasogastric tube, and a postpyloric feeding tube were in place. A portable high-frequency oscillatory ventilator was used to support her ventilation. The team then placed an oximetric pulmonary artery catheter. The patient was subsequently cannulated with catheters in the right internal jugular vein and right femoral vein. Venovenous ECMO therapy was started, and the patient was transported by ambulance to our facility.

**ECMO day 1, ventilator day 5**

Upon arrival at our hospital, the patient (EP) was taken for computed tomography (CT) scans of the head, chest, abdomen, and pelvis and was then admitted to the trauma and surgical intensive care unit (ICU). Venovenous ECMO was continued with an FiO2 of 1.00 via the pump oxygenator. High-frequency oscillatory ventilation was continued with the volume diffusive respirator set at an FiO2 of 0.50. The patient received a bedside bronchoscopy by the ECMO team and new culture samples (sputum, blood, urine, and nasal swab for H1N1) were obtained. The infectious disease team was consulted for antibiotic management.

EP's family arrived and was accompanied to the bedside by the chaplain. The family was tearful but appropriate as the gravity of EP's condition and the plan of care for the next hours and days were explained.

**Vital signs**

Heart rate, 105/min; mean arterial pressure (MAP), 80 mm Hg; diastolic pulmonary artery pressure (PAD), 26 mm Hg; central venous pressure (CVP), 17 mm Hg; cardiac index (calculated as cardiac output in liters per minute divided by body surface area in meters squared), 4; systemic vascular resistance (SVR), 650 dyne·sec·cm⁻⁵; mixed venous oxygen saturation (SvO₂), 84%; arterial oxygen saturation (SaO₂), 86%

**Laboratory test results**

Arterial blood gas analysis (ABG): pH, 7.40; PCO₂, 39 mm Hg; PO₂, 68 mm Hg; bicarbonate, 22 mEq/L; hématuricite, 33%; platelet count, 109 000/µL

**Medication infusions**

Midazolam, 5 mg/h; fentanyl, 100 μg/h; cisatracurium, 3 μg/kg per minute; norepinephrine, 5 μg/min; heparin, 2000 U/h; regular insulin, 10 U/h

**Blood products transfused**

Packed red blood cells (PRBCs), 3 units; platelets, 1 unit
The norepinephrine was tapered off overnight with MAP maintained between 70 and 80 mm Hg. EP required increasing doses of the cisatracurium, midazolam, fentanyl, and insulin. A nutritionist was consulted and total parenteral nutrition was started. Dressings at the cannulation sites began to saturate with blood, which required frequent dressing changes and reinforcement. Multiple units of PRBCs and platelets were transfused to keep the hematocrit and platelet counts above the prescribed levels.

**ECMO day 3, ventilator day 7**

EP was transported to the operating room for a tracheostomy. En route, a CT scan was obtained that showed dense consolidation of posterior lung fields with right-sided pulmonary embolism. The patient continued to bleed from the cannula sites. Diuresis was initiated with a furosemide infusion as the patient’s fluid balance was positive by 9 L.

**ECMO day 4, ventilator day 8**

Bleeding increased to a steady trickle from cannulation and tracheostomy sites. Hematuria was noted as well. The hematology service was consulted. Diuresis was moderately effective with urine output of 100-150 mL/h. The nephrology service was consulted. Hemofiltration was ordered and initiated via the ECMO circuit to remove fluid at a rate of 200-300 mL/h. Total parenteral nutrition was continued and trophic tube feedings were added via the postpyloric feeding tube.

**ECMO day 5, ventilator day 9**

EP’s oxygenation began to improve, evidenced by an increasing SpO2 in relation to the SvO2 as well as improving findings on chest radiographs. Continued but decreased bleeding was noted from all puncture and catheter sites. Hemofiltration was converted to continuous renal replacement therapy (CRRT) in order to facilitate clearance of toxins and electrolyte management and the furosemide infusion was turned off.

**ECMO day 6, ventilator day 10**

The first “trial off” procedure was performed. After 15 minutes with the ECMO oxygenator cuffed and the ventilator FiO2 at 100%, EP had a Pao2/FiO2 ratio of 260. The ventilator was then decreased to 50% for 15 minutes. A second sample was obtained for ABG analysis and the Pao2/FiO2 ratio had decreased to 190. The decision was made to continue ECMO support at this time. Adequate fluid removal was maintained with CRRT. Because of continued bleeding from cannula sites, EP continued to require the transfusion of PRBCs and platelets as well as

**ECMO day 2, ventilator day 6**

The norepinephrine was tapered off overnight with MAP maintained between 70 and 80 mm Hg. EP required increasing doses of the cisatracurium, midazolam, fentanyl, and insulin. A nutritionist was consulted and total parenteral nutrition was started. Dressings at the cannulation sites began to saturate with blood, which required frequent dressing changes and reinforcement. Multiple units of PRBCs and platelets were transfused to keep the hematocrit and platelet counts above the prescribed levels.

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frequent reinforcement of dressings. Hematology was consulted to assist with bleeding and coagulation management. EP’s condition began to tolerate minimum to moderate turning from side to side. Upon inspection of posterior body surfaces, a small stage 1 pressure sore was observed on the coccyx.

ECMO day 7, ventilator day 11
A second trial off was performed. With the ventilator FiO₂ set at 1.0, the PaO₂/FiO₂ ratio was 270. However, the PaO₂/FiO₂ ratio decreased to 210 after the ventilator FiO₂ was reduced to 0.50. Once again, ECMO support continued even though the required anticoagulation was continuing to produce significant bleeding from all cannula and catheter sites as well as notable hematuria.

ECMO day 8, ventilator day 12
A trial off procedure was performed again. Significant improvement was noted with a PaO₂/FiO₂ ratio of 285 after 15 minutes and 250 after 30 minutes. The risk benefit analysis of whether or not to decannulate was conducted. It was decided that the respiratory indicators were favorable enough in contrast to the risk presented by EP’s persistent bleeding, so EP was taken to the operating room for decannulation. After decannulation, EP was safely returned to the ICU with stable vital signs. With cessation of the heparin infusion, bleeding from all puncture and catheter sites became barely detectable. CRRT was continued via a dual-lumen dialysis catheter that was placed intraoperatively.

Ventilator day 13
Routine ICU standards of care resumed. With the cessation of ECMO, EP’s oxygenation and ventilation were supported solely with the ventilator set at an FiO₂ of 0.60. Bleeding was greatly decreased from cannula sites with the heparin infusion turned off. In addition, significantly less hematuria was observed. The cisatracurium infusion was discontinued. The infusions of fentanyl and midazolam were maintained at this time with a plan to begin weaning. The wound care team was consulted for assistance in managing the patient’s pressure sore. bedside bronchoscopy and chest radiographs showed improvement. EP’s management was transferred to the critical care medicine team.

Vital signs
Heart rate, 90/min; MAP, 75 mm Hg; PAD, 24 mm Hg; CVP, 13 mm Hg; cardiac index, 2.9; SVR, 950 dynes ·sec ·cm⁻⁵; SvO₂, 92%; SaO₂, 99%

Laboratory test results
ABG: pH, 7.45; PaO₂, 105 mm Hg; Pa₂, 105 mm Hg; bicarbonate, 26 mEq/L; hematocrit, 27%; platelet count, 70 000/µL

Medication infusions
Midazolam, 25 mg/h; fentanyl, 300 µg/h; cisatracurium, 6 µg/kg per minute; heparin, 2000 U/h; regular insulin, 75 U/h

Blood products transfused
PRBCs, 5 units; platelets, 3 units

Vital signs
Heart rate, 80/min; MAP, 85 mm Hg; PAD, 26 mm Hg; CVP, 15 mm Hg; cardiac index, 2.8; SVR, 1000 dynes ·sec ·cm⁻⁵; SvO₂, 92%; SaO₂, 100%

Laboratory test results
ABG: pH, 7.44; PaO₂, 125 mm Hg; Pa₂, 125 mm Hg; bicarbonate, 26 mEq/L; hematocrit, 31%; platelet count, 95 000/µL

Medication infusions
Midazolam, 25 mg/h; fentanyl, 300 µg/h; cisatracurium, 6 µg/kg per minute; heparin, 2000 U/h; regular insulin, 50 U/h

Blood products transfused
PRBCs, 2 units; platelets, 1 units

Vital signs
Heart rate, 100/min; MAP, 80 mm Hg; PAD, 24 mm Hg; CVP, 12 mm Hg; cardiac index, 2.8; SVR, 1050 dynes · sec · cm⁻⁵; SvO₂, 75%; SaO₂, 96%

Laboratory test results
ABG: pH, 7.41; PaO₂, 110 mm Hg; Pa₂, 110 mm Hg; bicarbonate, 23 mEq/L; hematocrit, 30%; platelet count, 102 000/µL

Medication infusions
Midazolam, 15 mg/h; fentanyl, 250 µg/h; cisatracurium, off; heparin, off; regular insulin, 30 U/h

Blood products transfused
None

Over the course of the subsequent 4 days, sedation was gradually weaned. Ventilator settings were adjusted down as the patient tolerated. Three days after decannulation, EP’s ventilator was changed to a conventional ventilator with settings of controlled mandatory ventilation at a rate of 14 breaths per minute and an FiO₂ of 0.45. On the fifth day after decannulation, EP began to consistently follow commands. The ventilator was progressively weaned and 2 days later EP had her first trial off of the ventilator.

Three days later, EP tolerated 24 continuous hours off of the ventilator. She continued to interact appropriately with staff and family and was out of bed to a chair with increasing frequency and duration each day. Two days later, she was transferred to the step-down unit with a grateful family at her side. It had been 19 days since she had been admitted to our hospital, and 24 days since she had first been admitted to the emergency department at the outlying hospital. Two weeks later, she was discharged home.
Unlike other critically ill patients, our ECMO patients did not receive daily sedation holidays because we were concerned that a patient might become agitated and thrash about in bed, dislodging a cannula. As a result, our neurological assessments were limited. Pupillary response was checked hourly and was our primary means of assessing for neurological changes. Computed tomography of the brain was done when any indication of a change in neurological status occurred or any time the patient left the unit for an operative or a diagnostic procedure. The rationale for such extreme vigilance in neurological monitoring was the concern for spontaneous intracerebral hemorrhage, which would be a critical contributing factor for the discontinuation of ECMO therapy.

Although it was our practice to maintain deep sedation and paralysis with these patients, anecdotal reports from other ECMO centers have led us to examine our practice. Many centers related the ability to manage ECMO patients at the same levels of sedation typical for other ICU patients (ie, a Riker score of 2-3).26 On the basis of this information, we will be more comfortable using the lightest appropriate level of sedation for future ECMO patients.

Cardiovascular Considerations

Monitoring and support of the cardiovascular system were essential. Systemic blood pressure, urine output, extremity temperature, capillary refill time, and strength of distal pulses were assessed hourly. Hemodynamic monitoring via a pulmonary artery catheter enabled us to optimize fluid status, cardiac output, and organ perfusion. Hemodynamic stability and tissue perfusion were maintained within patient-specific targets during venovenous ECMO. Interventions included judicious fluid replacement and titration of vasoactive medications.

At the time ECMO was started, patients often required volume replacement, a typical requirement of most patients with ARDS.28 Replacement was achieved with transfusion of blood products or the administration of crystalloid and colloid solutions. Our patients received the majority of their fluid replacement in the form of packed red blood cells, fresh-frozen plasma, and plateletpheresis units to maintain a hematocrit level of 32%, an international normalized ratio of 1.5, and a platelet count of 100 000/μL. Volume replacement was deemed adequate if central venous pressure was 9 to 12 mm Hg and pulmonary capillary wedge pressure was between 13 and 20 mm Hg. These parameters reflect our standard target range, although at times modification was required to meet specific patient requirements. When a patient remained hypotensive despite adequate fluid replacement, treatment with vasoactive medications was initiated. If a patient’s unstable hemodynamic status was judged to be due to poor cardiac performance, positive inotropic agents such as epinephrine, dopamine, and dobutamine were used. If the causative factor was vasodilatation as evidenced by low systemic vascular resistance, vasopressors such as norepinephrine and phenylephrine were added to the treatment regimen. Cardiac performance in patients treated with venovenous ECMO often improves rapidly because the improved oxygen delivery decreases myocardial workload. Patients usually can be quickly weaned off vasopressors. When adequate myocardial function cannot be maintained despite the interventions described, conversion to venoarterial ECMO is considered.24

Monitoring via a pulmonary artery catheter was started in each ECMO patient. We used the monitoring to determine trends in cardiac output and mixed venous oxygen saturation (SvO₂). Often, multiple thermodilution injections were required to acquire a consistent carbon output curve. This requirement most likely was due to the proximity of the ECMO drainage and return catheters to the right atrium, where the thermodilution injectate is infused.24

SvO₂ values are distorted during venovenous ECMO because of the presence of oxygenated blood in the right atrium.24 Values much greater than the normal range of 60% to 80% were common and were essentially the same as the arterial oxygen saturation (SaO₂) values. Therefore, we monitored SvO₂ for trends rather than for individual values to assess changes in oxygen delivery and consumption.23 We found that SvO₂ was more useful as a component of determining native lung recovery. (See the section “Respiratory Considerations.”)

Hematologic Considerations

The ECMO circuit presents a foreign surface, activating the clotting cascade and causing platelets to adhere to the surface of the extracorporeal circuit. These changes promote the release of additional substances that further platelet activation and aggregation. This cycle,
along with subsequent activation of fibrinolytic pathways in the ECMO circuit, results in consumption of clotting factors, impaired platelet function, thrombocytopenia, and fibrinolysis. In order to prevent the formation of clots within the ECMO circuit, full anticoagulation must be achieved. A bolus of heparin was administered intravenously immediately after cannulation, and heparin was infused for the duration of ECMO therapy. The bedside nurse or the perfusionist determined the activated clotting time at least hourly, and titrated the heparin infusion to maintain the time between 180 and 220 seconds.

Because of the use of systemic anticoagulants, frequent monitoring for bleeding is critical throughout the course of venovenous ECMO therapy. Simple bedside procedures such as venipuncture, finger sticks, endotracheal suction, and catheterization of the nose or urethra can precipitate refractory bleeding. Intracranial bleeding was the most serious potential complication of full anticoagulation and, when it occurred, was extensive and fatal. Any evidence of intracerebral bleeding on computed tomography was cause for discontinuation of ECMO. All venipunctures and other invasive procedures were completed before initiation of ECMO and were not resumed until treatment with anticoagulants was terminated (Table 3). Gastrointestinal bleeding was assessed by testing the output from nasogastric and rectal tubes for occult blood.

Significant oozing from cannulation sites required frequent dressing reinforcement and changes. Evaluations of hematocrit level, international normalized ratio, and platelet count were performed every 2 to 4 hours. Our protocol dictated maintaining the hematocrit level at greater than 32%, international normalized ratio at 1.5, and platelet count at 100,000/µL.

**Respiratory Considerations**

During venovenous ECMO, the lungs are not the primary site of gas exchange. Rather, this function occurs within the membrane lung of the ECMO circuit. In order to facilitate lung rest during ECMO, the mechanical ventilation was decreased to the lowest level that the patient would tolerate as indicated by arterial blood gas analysis, SatO₂, and PacO₂.

We use the volume diffusive respirator (VDR; Percussionaire Corp, Sandpoint, Idaho) for patients with severe respiratory failure (Figure 3). VDR ventilation is a form of high-frequency percussive ventilation that can be an effective salvage therapy for adults who have ARDS. The VDR ventilator provides time-cycled, pressure-limited ventilations at shallow tidal volumes and rapid rates that can reach or exceed 500/min. The primary benefits of high-frequency percussive ventilation include less barotrauma and increased lysis and clearance of airway secretions. Decreased barotrauma is thought to be due to lower peak inspiratory pressures and oxygen requirements than those in conventional ventilatory modes. Increased clearance of secretions most likely is due to the intrapulmonary percussive waves generated by this mode of ventilation. For our H1N1 patients treated with venovenous ECMO, we used VDR “rest settings” of fraction of inspired oxygen 40%, pulsatile flow 24 cm H₂O, oscillatory positive end-expiratory pressure 12 mm Hg, pulse frequency 500/min, convective rate 15/min, and an inspiration to expiration ratio of 1 to 1. These rest settings were maintained throughout therapy with ECMO and were generally not adjusted until ECMO weaning trials were conducted.

Treating acute respiratory failure with venovenous ECMO predisposes patients to a several lung-specific complications. Because ECMO patients vary widely between profound anticoagulation and hypercoagulable states, management of bleeding and its sequelae is a challenge. A frequent complication in our patients was bleeding from lung

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**Table 3** Catheters and tubes that must be in place before administration of anticoagulant for extracorporeal membrane oxygenation

<table>
<thead>
<tr>
<th>Catheter/Tube</th>
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<tbody>
<tr>
<td>Arterial catheter</td>
</tr>
<tr>
<td>Central venous catheter introducer</td>
</tr>
<tr>
<td>Oximetric pulmonary artery catheter (calibrated before extracorporeal membrane oxygenation started)</td>
</tr>
<tr>
<td>Postpyloric feeding tube</td>
</tr>
<tr>
<td>Gastric tube</td>
</tr>
<tr>
<td>Urinary catheter</td>
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<tr>
<td>Peripheral intravenous catheters</td>
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</table>
parenchyma due not only to the systemic anticoagulation but also to the H1N1 disease process.30 Assessment for pulmonary hemorrhage included monitoring of activated clotting times and levels of blood clotting factors, as previously discussed, and bronchoscopy. Bronchoscopy is an effective means of clearing thrombi that obstruct the tracheobronchial tree and is also vital for clearing airway secretions in patients with systemic paralysis.36

A second common complication was pulmonary emboli, which can occur in patients treated with ECMO despite systemic anticoagulation.30 Because our patients were already being treated with therapeutic levels of heparin, the ECMO team did not routinely pursue further treatment for pulmonary emboli. How pulmonary emboli can develop in the presence of significant levels of anticoagulant agents merits further investigation.

Pulmonary hypertension was yet another complication in some H1N1 patients. Because of the pathological changes associated with ARDS, secondary pulmonary hypertension can develop in patients who have no history of pulmonary disease. Secondary pulmonary hypertension is due to hypoxemia, which causes a ventilation-perfusion mismatch and leads to vasoconstriction and increasing vascular resistance.37 In H1N1 patients treated with venovenous ECMO, the most prevalent cause of hypoxemia is alveolar hypoventilation from alveolar destruction.10

The following advanced interventions for H1N1 patients with profound ARDS were at times beneficial. Intravenous milrinone and prostaglandin, as well as inhaled epoprostenol and nitric oxide, were used to promote vasodilation and enhance oxygenation. We assessed the effectiveness of therapy by determining the trends of pulmonary artery pressures and $S\bar{v}O_2$ values. Generally speaking, decreased pulmonary artery pressures in association with improved $S\bar{v}O_2$ values indicated a positive response to these measures.

Another intervention used for some patients was prone positioning. We attempted placing patients prone when the patients’ respiratory failure remained refractory to ECMO support as indicated by unchanged or worsening findings on chest radiographs and oxygenation indices. Placing patients prone, a delicate maneuver in the best of circumstances, became even more challenging in patients receiving venovenous ECMO therapy because of the possibility of accidental decannulation. Like many decisions in the care of these patients, whether to use prone positioning involved a careful analysis of risk vs benefit. The question What could possibly go wrong? became routine in our collective vocabulary as we developed strategies to manage and prevent worst-case scenarios. Unfortunately, we observed little improvement in oxygenation when patients were placed prone. This lack of improvement most likely was due to the profound and dense consolidation throughout their entire lung fields typical with H1N1 influenza.

Our usual standard of care for high-acuity patients was also modified in regards to tracheostomy. Typically, critically ill patients in our ICU do not have a tracheostomy until they have been receiving mechanical ventilation for 7 to 10
days. However, earlier tracheostomy for ECMO patients may help by ultimately allowing for decreased sedation.

Because of the decreased incidence of nosocomial pneumonia associated with tracheostomy vs oral intubation, the Extracorporeal Life Support Organization recommends early tracheostomy if a patient is not expected to be weaned from ECMO within a few days. The decision to convert from endotracheal tube to tracheostomy required the care team to carefully assess the benefits of early tracheostomy vs the risk of potential bleeding when this procedure is performed on a patient treated with anticoagulants.

In addition, the physical location of the tracheostomy was a subject of important discussion. Risks and benefits of bedside percutaneous tracheostomy were weighed against traveling to the operating room. If a patient had to travel outside the ICU for any operative or diagnostic procedure, the tracheostomy was performed in the more controlled environment of the operating room. Otherwise, bedside percutaneous tracheostomy was performed in the ICU to avoid subjecting the patient to the risks of transportation. In either situation, the surgical team was forced to proceed cautiously and to carefully manage bleeding.

As venovenous ECMO continued, the H1N1 patients were monitored for any evidence of lung recovery that suggested weaning from extracorporeal support might be possible. The primary indication of lung recovery was a “step-up” across the pulmonary membrane. As previously described, during venovenous ECMO, oxygenation and ventilation occur in the extracorporeal lung because the damaged native lungs cannot contribute to this process. \( S\text{\textsubscript{VO}}_2 \) as measured by pulmonary artery catheter was essentially equal to the \( \text{Sao}_2 \). As a patient’s native lung function improved and contributed to gas exchange, the \( \text{Sao}_2 \) increased with respect to the \( S\text{\textsubscript{VO}}_2 \), thus providing the step-up across the native lung membrane. Additionally, bronchoscopy findings and portable chest radiographs were evaluated daily for evidence that the patient’s lungs were improving.

Once a patient began to have evidence of lung healing and recovery, a “trial off” procedure was performed at the bedside. The trial off is a mechanism to assess a patient’s native lung function. For this assessment, the ECMO attending physician, respiratory therapist, perfusionist, and bedside nurse were present. The ventilator was set to a fraction of inspired oxygen of 100% with the pulsatile flow rate and oscillatory positive end-expiratory pressure set at an optimal level as determined by the respiratory therapist. The ECMO circuit was then set to provide a minimal level of support.

In order to prevent coagulation of the ECMO circuit, blood must continue to flow through the tubing. This flow is achieved in 1 of 2 ways. The oxygenator can be “capped,” which removes the gas flow from direct contact with the blood and thus stops extracorporeal oxygenation and carbon dioxide clearance. In the second method, the ECMO blood flow is reduced to a rate that will not markedly contribute to gas exchange, yet still provides enough flow to prevent the circuit from clotting. With the oxygenator capped or the flow drastically reduced, the patient’s native lungs once again became the primary site of gas exchange. Throughout the trial, vital signs were monitored. The procedure was terminated for \( \text{Sao}_2 \) less than 92% or any indications of unstable respiratory or hemodynamic status. After 15 minutes, blood for arterial blood gas analysis was obtained from the patient’s arterial catheter and evaluated. If the ratio of \( \text{Pao}_2 \) to fraction of inspired oxygen was less than 250, full ECMO support was resumed, and the ventilator was returned to the previous rest settings. If the ratio was greater than 250, the fraction of inspired oxygen of the ventilator was reduced to 50%, and the patient was observed for an additional 15 minutes and a second sample for arterial blood gas analysis was obtained. If the ratio after the 30-minute trial remained greater than 250, the team gathered to determine whether decannulation was appropriate.

If the decision was made to stop ECMO therapy and remove the cannulas, the next concern became determining the safest method to use. Often, venous cannulas were successfully removed at the bedside by the attending physician, with direct pressure subsequently applied for a minimum of 15 minutes. If a patient had an elevated risk for hemorrhage or a need for vascular repair, the patient and entourage of equipment were transported to the operating room for surgical removal of the cannulas and definitive control of any marked bleeding.

### Renal Considerations

Acute renal insufficiency or failure is an undesired but not unexpected complication in patients who...
require aggressive cardiopulmonary support, replacement of large volumes, and vasopressor therapy. Spontaneous or pharmacological diuresis was used in our ECMO patients until optimum or dry weight returned and edema cleared. Hemofiltration and continuous renal replacement therapy (CRRT) were important adjunctive therapies when diuretics alone were unsuccessful for fluid removal. Consultation with the nephrology service was obtained early in the course of ECMO therapy; the goal was a negative hourly fluid balance as tolerated to maintain systolic blood pressure greater than 100 mm Hg or mean arterial pressure greater than 60 mm Hg.

Tubing for hemofiltration and CRRT can be incorporated into the ECMO circuit by the perfusionist. If fluid removal alone is desired, a hemofilter can be placed directly into the ECMO circuit between the high-pressure arterial side and the low-pressure venous side. If electrolyte management and toxin clearance are also indicated, a CRRT machine can be added by using the ECMO circuit itself to provide the sites for blood access and return. We found that configuring CRRT to ECMO created access and return pressure readings greater than usual for the CRRT machine, resulting in numerous problems. The CRRT machines were prone to frequent alarms indicating increased filter pressures, as well as abnormal access and return pressures, creating the need for frequent restarts and dialysis circuit and filter changes. Filter pressure increases and the need for frequent filter replacement were probably due to clogging by large mediators of inflammation and sepsis. Occlusion due to clot formation was unlikely because of the systemic anticoagulation. Hemofiltration and CRRT resulted in euvolemia relatively easily despite the frequent filter changes. Cessation of hemofiltration and CRRT was indicated once euvolemia was achieved and/or when the patient’s urine output increased and the serum levels of urea nitrogen and creatinine normalized.

**Metabolic Considerations**

Addressing metabolic demands and glycemic control for patients on ECMO because of pneumonia due to H1N1 influenza A was challenging. Although a registered dietician calculated the caloric requirements for our patients according to the standards for a critically ill patient receiving paralytic agents and mechanical ventilation, we were unsure if the patients’ actual needs were being met. Ordinarily, a metabolic cart (a computerized instrument that uses calorimetry to measure metabolic energy expenditure) and 24-hour urine studies provide data for this calculation. However, use of the VDR ventilator and our patients’ relative oliguria obscured this data.

Total parenteral nutrition was routinely started on day 2. Lipid-free nutritional formula was infused because of concern about clogging the ECMO oxygenator. A postpyloric feeding tube was placed before anticoagulant was administered and ECMO was started. Trophic enteral feedings of free amino acids at a rate of 10 to 20 mL/h were started as soon as possible to preserve gut integrity and prevent bacterial transmigration into the bloodstream. We did not increase feedings to goal rates because of the risk of aspiration associated with the supine positioning required by the placement of femoral catheters. In the future, with increased use of dual-lumen cannulas placed solely in the jugular vein, we will strive to elevate the head of the bed to quickly reach goal rates for tube feedings and the enteral nutrition needs for ECMO patients.

Glycemic control in the H1N1 patients was surprisingly difficult. Blood glucose levels of 250 to 300 mg/dL (to convert to millimoles per liter, multiply by 0.0555) persisted despite continuous insulin infusion rates as high as 300 U/h. Also confusing was the lack of change in blood glucose levels despite drastic decreases in the insulin infusion. Different combinations of insulin were used, including regular insulin, insulin aspart (rDNA origin) injection (Novolog R), and insulin gareine (rDNA origin) injection (Lantus R).

At the time, we searched the literature for information on the adsorption of insulin onto the ECMO circuit because other drugs such as fentanyl adsorb to the polyvinylchloride tubing. We found no data specific to insulin; however, we learned from anecdotal reports of our ECMO colleagues around the United States that our experience was not unusual. This problem with glycemic control is yet another anomaly that merits further investigation.

**Family Support Considerations**

Because of the severity of H1N1 influenza A and the gravity of the situation, patients’ family members experienced a gamut of emotions. Honesty with the families was
imperative, and conversations about procedures, risks, complications, and code status were ongoing. In support of family-centered care, considerable time was allotted for the families to spend with their loved one. Involving a patient’s family in rounds was challenging in this circumstance because the shared information was often overwhelming and confusing. The multidisciplinary conversation associated with developing the plan of care was occasionally interpreted as uncertainty by patients’ family members. Bedside support included frequent, repetitive, and simple explanations by nurses and doctors to update the family members. Hospital chaplains and social workers offered spiritual and emotional support so that our primary focus could be to provide care for the patients.

Most ECMO patients who recover have minimal long-term physical complications. However, nurse researchers at the University of Michigan Hospital, Ann Arbor, Michigan, found that some patients experience psychological difficulties after ECMO. Like other critically ill patients, ECMO patients who make a full physical recovery often still see themselves as fragile and unable to handle the activities of everyday life. Spiritual and emotional support for our ECMO patients continued throughout their hospitalization. In addition, personnel from physical therapy, occupational therapy, and social services were available as needed to assist with return to the activities of daily living.

**Operational Considerations**

**Transportation Out of the ICU**

Looking into the room of an ECMO patient during this crisis was daunting. The physical space of the ICU room was overwhelmed by the amount of equipment necessary to care for these patients. Many times the patient needed to travel within the hospital for diagnostic tests or procedures that could not be done at the bedside. Communication and planning were the keys to a successful trip. Some of the equipment operated on battery power, some required additional tanks of oxygen, and some needed to be discontinued. Consideration of catheter placement, tubing length, and physical space in the hallways and diagnostic rooms is standard for any ICU patient’s intrahospital travel. Traveling with ECMO patients raised these concerns exponentially. With each excursion, the team had to ask, What could possibly go wrong with a portable lung machine connected via 2 large-bore cannulas inserted into 2 major vessels? Each trip was carefully planned and well thought out, and worst-case scenarios and solutions were carefully discussed beforehand. Even so, we quickly realized that more people did not equal better results, and we developed traveling guidelines that specifically designated roles and a team leader (Figure 4). If any computed tomography was ordered, we made sure to image as many organs as possible to reduce unnecessary trips. Returns to the operating room were also carefully considered, and risks were weighed as to which procedures could be done safely at the bedside.

**Staffing**

Each ECMO patient required 2 nurses, and smooth teamwork was essential (Table 4). Despite an 18-year experience with ECMO therapy for 1 to 2 patients per year, a designated protocol for an extreme situation with multiple simultaneous ECMO cases did not exist. We scrambled to coordinate staffing and formulate care standards and order sets to help daily operations run smoothly. In the past, nurses certified to care for patients after open heart surgery had been the primary nurses for ECMO patients. However, during this crisis-level situation, the demand for experienced ECMO nurses quickly surpassed the supply. Despite the steep learning curve, on-the-job training quickly prepared additional experienced ICU nurses to help care for these patients.

The increased demand on nursing staff to care for so many high-acuity patients in such a short time was physically and emotionally exhausting, and many hours of overtime were logged. Although staff fatigue was sometimes evident, our nurses were resilient and dedicated. In the end, everyone persevered to provide the best possible patient care. When the dust settled, a debriefing was held for the entire team. Frustrations were vented, tears were shed, and thanks and praise were given and received. Lessons learned were openly discussed, and an enthusiasm to do better next time was universal.

**Resource Considerations**

The H1N1 influenza A epidemic depleted more than staffing. The supplies used during the H1N1 surge drained the entire 5-hospital system. Because we placed all H1N1 patients in droplet isolation, and the health care team was so large, related supplies and personal protective equipment were rapidly
Our facility used 2 to 3 times more supplies, including masks, isolation gowns, laboratory tubes, machines to determine activated clotting time, and syringes than in the same period the previous year. We even had a shortage in alcohol foam hand disinfectant by the time the surge peaked.

The ECMO team had daily briefings with hospital administration and the unit’s medical director. Patient census, potential referrals to the ICU, triage planning, and availability of medications and respiratory equipment and general supplies were reviewed. A strategic plan for each 24-hour period was developed to ensure adequate resource allocation.

Looking Back and Looking Ahead

What lessons did we learn? In the months since the H1N1 crisis passed, we have had the opportunity to reflect on our response, identify areas for improvement, and provide education for our nurses to prepare for subsequent influxes of ECMO patients. In many instances, the crisis of the H1N1 illness prompted us to deviate from ideal standards of care. Briefly stated, our primary lesson learned was to approach sedation management of ECMO patients in a manner more consistent with that used for other ICU patients. With increased use of the single dual-lumen venovenous ECMO cannulas, which are less likely to become dislodged than are 2 single-lumen catheters, care can include daily sedation interruptions and decreased levels of sedation. The freedom provided by a single access point in the neck will also

Table 4 Duties of the 2 nurses assigned to each patient receiving extracorporeal membrane oxygenation for treatment of H1N1 influenza A

<table>
<thead>
<tr>
<th>Primary nurse</th>
<th>Second nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do a head-to-toe assessment of the patient</td>
<td>As able, perform tasks delegated by the primary nurse</td>
</tr>
<tr>
<td>Document results of laboratory tests, vital signs, and assessment</td>
<td>Titrate drugs as indicated by the primary nurse</td>
</tr>
<tr>
<td>Document on computer intravenous infusions, teaching, and plan of care</td>
<td>Obtain all samples for laboratory tests</td>
</tr>
<tr>
<td>Communicate with the patient’s family, provide updates, and answer questions</td>
<td>Assist in checking blood products</td>
</tr>
<tr>
<td>Delegate tasks and procedures to the second nurse</td>
<td>Start infusion of blood products</td>
</tr>
<tr>
<td>Write down physician’s orders given by telephone or verbally</td>
<td>Sign standards of care at the end of each shift</td>
</tr>
<tr>
<td>Order blood products as ordered by the physician</td>
<td></td>
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</tbody>
</table>
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Figure 4 Guidelines for transporting patients receiving extracorporeal membrane oxygenation (ECMO).
permit us to elevate the heads of patients’ beds to facilitate enhanced pulmonary hygiene and enable the advancement of enteral nutrition with less risk for aspiration.

Finally, in an effort to provide more efficient care to larger numbers of ECMO patients in the future, our hospital is expanding the ECMO program. With the goal of improved resource utilization, the 2 separate adult and pediatric ECMO programs are being combined. In order to be consistent with the existing practice in the hospital’s pediatric and neonatal ICUs, a cohort of adult ICU nurses are training to be ECMO specialists. The plan is for all ECMO patients, once their condition is stabilized after cannulation, to have their care managed by 1 nurse ECMO specialist and 1 bedside nurse.

Summary

The critical care staffing crisis created by the H1N1 influenza A epidemic cannot be overstated. It is one thing for a 14-bed ICU to care for a single ECMO patient at a time, once or twice a year. It is quite another for that same unit to go, overnight, from 1 patient receiving ECMO to 4 patients receiving ECMO simultaneously. Because of the ingenuity and resiliency of our multidisciplinary team, 9 patients survived who would not have otherwise lived. Although we still have areas for improvement in our delivery of care for patients treated with ECMO, as a whole, we are proud of our response to this profound challenge. By describing both our successes and areas for improvement, we hope that other health care teams and hospital systems can benefit from our experiences. CCN

References


