Editorial

Uncertainties on the Frontier: Rescue Therapy in Pandemic Influenza

By Cindy L. Munro, RN, PhD, ANP

The following posting to a critical care electronic discussion group generated much discussion but no resolution to the writer's dilemma:

> We are a small community hospital, but we have treated patients with H1N1 influenza. We are getting pressure to use ECMO [Extra Corporeal Membrane Oxygenation] as an option in treating the sickest of these patients, but we don't see much evidence in the literature for its use in H1N1 influenza, and we don't really have any expertise in this area. We are torn between trying to do everything possible to save these patients and accepting that there may be technologies we cannot realistically use. Help!

This note echoes frank discussions providers have at professional meetings and in the hallways where they practice. H1N1 influenza gives a new twist to these discussions, but the problems of what to do when all else has failed, and of how and when to introduce new technology, have resonated throughout the history of critical care.

The H1N1 influenza pandemic, which began in the spring of 2009, has presented providers with numerous challenges. In contrast to typical seasonal influenza from which elders and those with preexisting illnesses are more likely to become ill and die, H1N1 sickens and kills young people. Early in the pandemic, the "usual course" of the disease, its complications, and response to standard treatment were all unknown. Some patients admitted to the intensive care unit (ICU) with H1N1 influenza had a disturbingly rapid deteriorating course and continued worsening despite aggressive conventional therapy.

A qualitative study[1] of Australian providers' experiences in caring for H1N1 patients highlighted the emotional difficulty in dealing with the young age of the patients and the unpredictability of the disease; demands of ECMO therapy was 1 of 8

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themes identified as problematic for bedside providers in the qualitative data.

ECMO and "Rescue" therapy

ECMO was developed clinically in 1954 as an intraoperative technique to support patients during cardiac surgery, and was first used to treat a trauma patient with acute respiratory distress syndrome (ARDS) in 1971.[2] Since that time, ECMO has demonstrated its value in pediatric intensive care and is a common therapy for neonates and children requiring cardiopulmonary support.[3] Research to evaluate the effectiveness of ECMO has been difficult to perform and ethically controversial.[4,5]

Unfortunately, clinical trials of ECMO for treatment of ARDS in adults in the 1970s were disappointing, tainting its use for many years. However, as advancements have been made in the care of mechanically ventilated patients and in ECMO technology, there has been a renewed interest in investigations of ECMO in ARDS. A very recent large, multicenter, randomized controlled trial conducted in the United Kingdom, conventional ventilation or ECMO for severe adult respiratory failure (CESAR),[6] demonstrated better survival without disability at 6 months in those who were randomized to receive ECMO compared to those who received usual intensive care.

It is not surprising that rescue therapies, including ECMO, have featured prominently in early accounts of H1N1 treatment. There simply had not been time to conduct the research in this population at the point where providers were faced with selecting from a limited number of therapeutic options. Decision making often occurred in a context in which conventional therapies were failing and there was little left to offer the patient and family. In Australia and New Zealand, during the Southern hemisphere winter months of 2009 (June to August), about 12% of all patients with H1N1 who were admitted to an ICU received ECMO[7]; for institutions where ECMO was offered, a third of all H1N1 ICU patients were treated with ECMO. Interestingly, during roughly the same period in Canada (April to August 2009; spring and summer in the Northern hemisphere), ECMO was instituted for only 4.2% of ICU patients with H1N1.[8]

Other rescue therapies have been suggested for patients with H1N1 influenza and a worsening condition, including high-frequency oscillatory ventilation, prone positioning, neuromuscular blockade, inhaled nitric oxide, prostacyclins, corticosteroids, and exogenous surfactant.[8,9] In Canadian data, several other rescue therapies were reported more commonly than ECMO, including neuromuscular blockade (28% of patients), inhaled nitric oxide (13.7%), and high-frequency oscillatory ventilation (11.9%).[8] An algorithm for use of rescue therapies in ARDS was recently proposed; extracorporeal interventions are suggested to follow other, less invasive strategies.[10]

Risk and Benefit

Because rescue therapies are employed at the point of failure of conventional therapy, it is difficult to assess risk and benefit. The results of the CESAR trail were published in November 2009, months after the first wave of critically ill H1N1 influenza patients were treated with ECMO. Assessment of potential benefit for an individual patient frequently occurs on a case-by-case basis, in which case any benefit would seem to outweigh the risk of imminent death. Often, the calculation of risk and benefit must be extrapolated from previous indications and experience; such extrapolations may or may not accurately reflect the new situation.

The outcomes obtained in individual cases influence providers' beliefs about the efficacy of a particular rescue therapy and its subsequent wider adoption. If we see a patient improve following an intervention, we are convinced that the intervention contributed to the good outcome and has merit. Conversely, if our patient does not survive following the same intervention, we may be inclined to think that death was inevitable. We must be careful to remember that our own experience in individual cases does not provide generalizable evidence. Wolfson et al,[11] in a report of ECMO used as rescue therapy for an adolescent post-stem cell transplant, summarizes this dilemma:

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> Obviously, the good outcome in this case does not prove that ECMO will be beneficial in all cases of sepsis with hemodynamic instability after stem cell transplantation. Similarly, a bad outcome would not have proven that ECMO was inevitably futile in such cases.

There are certainly examples where novel technology turns out to be life saving and becomes standard of care. There are also examples that serve as cautionary tales, in which therapies with great promise based on efficacy in a particular population are no help (or are harmful) in a different population. The story of rescue therapy for breast cancer using high-dose chemotherapy with autologous bone marrow transplant provides such a warning.[12]

During the 1980s, with few effective treatments for aggressive breast cancer and small studies that hinted high-dose chemotherapy with autologous bone marrow transplant might help, both oncologists and patients became enthusiastic about this highly toxic and risky intensive rescue therapy. Insurance companies resisted payment based on a lack of convincing evidence that the therapy was effective. Unfortunately, randomized clinical trials showed that high-dose chemotherapy with autologous bone marrow transplant was no better than (and was perhaps worse than) standard treatment at the time.

Issues of Expansion

Additional research and experience may uphold the conclusions of the CESAR trial that ECMO is beneficial in ARDS. If so, use of the technology in the adult critical care setting is likely to expand. In the data reported from Australia and New Zealand, only 4 patients received ECMO for ARDS in 2008; 61 patients were treated during the same period in 2009.[7] Whereas this increase was attributed to the large number of H1N1 influenza cases, it seems likely that ECMO use will continue to increase beyond 2008 levels. The complexity of ECMO has led to its concentration in centers with specialty expertise in the technology. As the procedure continues to diffuse into critical care practice, there will be increasing pressures to expand the number of institutions where ECMO is offered.

Haile and Schears[13] describe ECMO as "by far the most complex life-sustaining technology employed." Successful implementation of ECMO is staff intensive and requires services of a perfusionist, anesthesiologists and critical care physicians with specialty knowledge, and nurses with expertise in care of both the patient and the equipment. Such expertise is most easily developed and maintained in settings where the procedure is performed frequently. Even in settings with substantial experience in ECMO, the procedure remains complex and personnel intensive. Peek and colleagues[6] argue that

> [p]rovision of ECMO will probably be most clinically and economically efficient (reduced cost per successful case treated) in large critical care units, and the clinical effectiveness of small units would be lower than that of busy units.

ECMO places substantial demands on bedside caregivers under ideal circumstances, and increased numbers of patients exacerbate these demands. Corley et al[1] documented nurses' concerns that established ECMO procedures and staffing were unable to be met during the patient surge of the Australian summer of 2009, and that staff distress accompanied the high demands in an environment of unmatched resources. Safety issues related to novel technology include communication among providers, technical competence of staff, and staffing. These factors are heavily influenced by how healthy the work environment is, and will influence whether an individual unit can safely incorporate novel technologies.

ECMO is an expensive procedure, both in personnel time and in money. Although the CESAR trial included a cost analysis component, the investigators acknowledge that their United Kingdom data cannot be applied to other health care systems. A host of factors that are unique to each health care system (including patient severity of illness, treatment outcomes, structure of the health care system, and costs) preclude generalizations about the cost effectiveness of ECMO in the United States. As health care reform progresses and cost-benefit ratios of treatment undergo enhanced scrutiny, additional research regarding costs of ECMO is warranted.

What to Do?

At the heart of the quote that opened this editorial are 3 questions for individuals and institutions to consider. First, what can we do? Answering this requires exploring all of the possible options, including those with which we may have less experience. Second, what can we do that will help? This question

acknowledges the tension between our desire to improve the patient's likelihood of a good outcome and the desire to do no harm. It is answered in light of the best available evidence, accepting that even the best evidence may be imperfect and will certainly change as more research is reported. Third, what can we do well? Here, we need to examine not only what is theoretically possible, but what is possible given the desire to maximize good outcomes and do no harm. Examination of these questions may mean that the best option will be to transfer the patient to an institution where more is possible, or it may mean concerted efforts to expand the repertoire of things we do well.

Critical care has always operated on the frontiers of health care. Struggles associated with the use of new technology, or older technology in new circumstances, will continue to challenge us. Procedures that were cutting edge a decade ago are commonplace now, and the trend to disseminate extraordinary interventions into routine practice is likely to continue. As we expand the boundaries of care for the critically ill, we will need thoughtful deliberation about what our individual units can accomplish and what will be in the best interest of patients, their families, and society in general.

The statements and opinions contained in this editorial are solely those of the coeditor.

FINANCIAL DISCLOSURES
None reported.

REFERENCES

1. Corley A, Hammond NE, Fraser JF. The experiences of health care workers employed in an Australian intensive care unit during the H1N1 influenza pandemic of 2009: a phenomenological study. *Int J Nurs Stud*. 2009; Dec 24. [Epub ahead of print].
2. Bartlett RH. Extracorporeal life support: history and new directions. *ASAIO J*. 2005;51(5):487-489.
3. Cooper DS, Jacobs JP, Moore L, et al. Cardiac extracorporeal life support: state of the art in 2007. *Cardiol Young*. 2007;17(S2):104-115.
4. Wolfson PJ. The development and use of extracorporeal membrane oxygenation in neonates. *Ann Thorac Surg*. 2003;76(6):S2224-2229.
5. Crow S, Fischer AC, Schears RM. Extracorporeal life support: utilization, cost, controversy, and ethics of trying to save lives. *Semin Cardiothorac Vasc Anesth*. 2009;13(3): 183-191. Epub 2009 Aug 26.
6. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilator support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363.
7. ANZIC Influenza Investigators, Webb SA, Pettilä V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med*. 2009;361(20): 1925-1934.
8. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA*. 2009;302(17):1872-1879.
9. Napolitano LM, Park PK, Raghavendran K, Bartlett RH. Nonventilatory strategies for patients with life-threatening 2009 H1N1 influenza and severe respiratory failure. *Crit Care Med*. 2009; Dec 23. [Epub ahead of print]
10. Deja M, Hommel M, Weber-Carstens S, et al. Evidence-based therapy of severe acute respiratory distress syndrome: an algorithm-guided approach. *J Int Med Res*. 2008;36(2):211-221.
11. Wolfson RK, Kahana MD, Nachman JB, Lantos J. Extracorporeal membrane oxygenation after stem cell transplant: clinical decision-making in the absence of evidence. *Pediatr Crit Care Med*. 2005;6(2):200-203.
12. Jacobson PD, Rettig RA, Aubry WM. Litigating the science of breast cancer treatment. *J Health Polit Policy Law*. 2007; 32(5):785-818.
13. Haile DT, Schears GJ. Optimal time for initiating extracorporeal membrane oxygenation. *Semin Cardiothorac Vasc Anesth*. 2009;13(3):146-153.