



A conceptual approach to improving care in pandemics and beyond: Severe lung injury centers

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Abstract The events of the 2009 influenza pandemic sparked discussion regarding the need to optimize delivery of care to those most severely ill. We propose in this conceptual study that a tiered regionalization care system be instituted for patients with severe acute respiratory distress syndrome. Such system would be a component of national pandemic plans and could also be used in day-to-day operations.

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In October of 2009, a 25-year-old man with no significant medical history presented to an emergency department in a community hospital rural Pennsylvania with 3 days of fever, myalgias, and severe progressive dyspnea. Chest radiography revealed diffuse bilateral infiltrates. On 100% nonrebreather mask, the patient had a PaO₂ of 60 mm Hg. The patient was admitted to the intensive care unit (ICU), intubated, and placed on mechanical ventilation. A rapid test for influenza A was positive, and he was started on oseltamivir. The patient's condition continued to deteriorate, and increasing levels of FIO₂ and positive end-expiratory pressure were used to a vain attempt to maintain adequate oxygenation. After 4 days on mechanical ventilation, the patient was transferred to a tertiary care medical center for consideration of rescue therapies.

Stories similar to this vignette occurred in many places worldwide during the 2009 H1N1 influenza pandemic in

which young adults and children were disproportionately affected by severe pneumonia. This shift in severe morbidity and mortality rates to younger age cohorts (compared with seasonal influenza) is typical of influenza pandemics. It was seen in each of the pandemic years for which we have detailed data, 1918, 1957, 1968, and 2009 [1]. In nonpandemic years, most life-threatening complications of influenza occur in infants and the very old and especially in individuals with multiple comorbidities—the archetype is a frail elderly person with chronic heart, lung, and/or renal disease [2]. In a series of informal interviews we conducted with intensivists from leading centers around the country about the 2009 pandemic, what is most vividly described is the large number of otherwise healthy young adults and children in their ICUs with respiratory failure and the extraordinary measures that were used in many cases to save their lives. Because this scenario is likely to be repeated in future pandemics, clinicians, hospitals, and health care planners should consider how best to optimize the delivery of the country's finite capacity for highly sophisticated care

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of severe respiratory failure, especially for those who are most likely to benefit—relatively young people with limited preexisting health problems.

In many communities, systems have been created to ensure that the transfer process for patients with strokes, heart attacks, and severe trauma occurs in a relatively predictable and efficient manner. In addition, transfer to specialty centers that can provide extracorporeal membrane oxygenation (ECMO) is the norm for severe respiratory distress in neonates. This routinizing of transfer protocols could be extended to severe acute respiratory distress syndrome (ARDS), as well, complementing the existing structures currently in place and harnessing the power of regional hospital coalitions, which have the capability to coordinate information exchange and have developed detailed regional care plans for public health emergencies.

1. The 2009 H1N1 pandemic experience

Although most people infected with pandemic H1N1 during the 2009 influenza pandemic had mild illnesses no worse than seasonal flu, a small minority of people developed ARDS. Because hundreds of millions of people were infected, this small percentage translated to a significant absolute number. Because no specific tally of ARDS cases attributed to the H1N1 pandemic was recorded, it is impossible to know precisely how many cases there were. However, estimates can be made based on several assumptions. According to a US case series of ICU patients infected with 2009 H1N1, 38% developed ARDS and 24% of patients with ARDS died [30]. It is estimated that 1 in 10 000 patients with pandemic H1N1 died of ARDS, and with 61 million estimated H1N1 cases in the United States, approximately 6100 ARDS deaths may have occurred [3,4]. This correlates with the Centers for Disease Control and Prevention's estimate of approximately 11 000 H1N1-related deaths in the United States during the pandemic [5]. Assuming a mortality rate from ARDS of 25%, an estimate of 24 400 ARDS cases in the United States secondary to pandemic H1N1 seems reasonable [6]. In many cases, these patients were young and otherwise relatively healthy. Because this was the first pandemic to occur in the age of modern critical care and the pandemic disproportionately affected the young—as pandemics usually do—aggressive modalities of treatment were used in severe cases in an effort to save the lives of individuals who could, potentially, go on to live for several decades.

There are anecdotal reports of several referral hospitals that were nearly overwhelmed for a time during the autumn wave of the pandemic (R. Bartlett, personal communication, December 2011). Clinicians at these facilities have indicated that more coordination of referrals might have helped to relieve the stress the facilities experienced. Conversely, there were also many anecdotes of patients with severe ARDS who were transferred too late to benefit from the highly specialized care available at referral centers.

2. Therapies for severe ARDS

The standard treatment of ARDS is lung protective ventilation, a ventilator strategy that has been shown to significantly decrease mortality rates from ARDS, and a fluid restrictive strategy management, which increases ventilator-free days [7,44]. In severe cases of ARDS, lung protective ventilation may be augmented by one or more advanced modalities including prone position ventilation, inhaled nitric oxide, inhaled prostacyclin, and high-frequency oscillating ventilation [8]. These are often called “rescue” therapies because they tend to be used when standard ventilation fails to sustain normoxia. Although each of these therapies has been shown to improve oxygenation, none has been shown to improve survival in patients with severe ARDS [9].

3. Extracorporeal membrane oxygenation in severe ARDS needs further validation

One advanced treatment modality that has been shown to potentially improve survival rates is ECMO. Extracorporeal membrane oxygenation involves placing a patient with intractable hypoxemia on a variation of a heart-lung machine that provides effective gas exchange while sparing the lungs from exposure to dangerously high pressures and/or oxygen concentrations on mechanical ventilation. Extracorporeal membrane oxygenation has been a standard treatment for respiratory failure in neonates since the 1990s. Past studies of ECMO in adults with respiratory failure failed to show any benefit. However, in the recent CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) trial, conducted in the modern era of lung protective ventilation and newer ECMO technology, adults with severe respiratory failure were randomized to conventional care or transfer to an ECMO center. The results revealed that those treated at ECMO centers showed a 16% increase in 6-month survival without disability, despite the fact that only 75% of those transferred to an ECMO center actually received ECMO [10]. A caveat to the CESAR trial is the fact that only 70% of control group patients received lung protective ventilation, significantly less than in the other arm [10]. Overall, the use of this modality has been increasing, and in 2002 to 2006, at least 600 adult patients were placed on ECMO for refractory respiratory failure [11]. These 600 patients had a survival rate of 50%; however, it can be assumed that because ECMO was used as a last resort when standard treatment failed, the fatality rate would have exceeded 50% without ECMO [11].

The CESAR study showed that patients transferred for ECMO benefited in terms of survival even if they do not receive ECMO. Presumably, this was because ECMO is usually performed only at high-volume referral hospitals where other types of expert care—including the increased presence of intensive care specialist physicians—are also available [12,26,27]. In fact, mortality rate differences among

the highest- and lowest-volume centers performing mechanical ventilation vary by close to 10%—a figure that could translate into thousands of lives saved when applied to the 190 600 ARDS cases that occur annually in the United States—a finding seen with other forms of medical care [6,12]. In a modeling study using these parameters and the discharge data from 8 US states, it was shown that 4720 lives could be saved in these 8 states by simply transferring mechanically ventilated persons from low- to high-volume centers—translating to a number needed to treat of 15.7 (ie, 15.7 additional transfers would result in 1 additional life saved) and a median travel distance of only 8.5 miles [41]. Similarly, volume-mortality benefits were found in the treatment of pneumonia—the precondition to ARDS in influenza [45]. Separating the benefit of expert care from the benefits of ECMO is a key research question that requires an answer. International ECMO trials are currently underway attempting this task.

4. Extracorporeal membrane oxygenation and H1N1

In the Southern Hemisphere, it was estimated that one third of hospitalized patients who required mechanical ventilation progressed to require ECMO [13]. In the United States, according to the Extracorporeal Life Support Organization (ELSO), more than 300 patients received ECMO, 65% of whom survived [14]. In the United Kingdom, mortality was reduced by 55% when patients with influenza were transferred to ECMO centers, although 14% did not ultimately receive ECMO [15]. One recent study, however, shows similar mortality rates during the pandemic in those with severe ARDS who received ECMO when compared with those who were ECMO eligible [42]. In addition to these locations, ECMO support of patients with influenza occurred in multiple locations throughout the world [13,16,17]. The worldwide use of ECMO among mechanically ventilated patients with pandemic H1N1 was estimated to be 4% to 9% [25].

5. A national tiered system for the care of severe ARDS for pandemics

The experience during the 2009 pandemic of stress on some ICUs and the increased use of ECMO sparked discussions about whether there might be a benefit in a more organized regionalization scheme for highly sophisticated intensive care (which may or may not include use of ECMO) [18–20]. This regionalization might facilitate more timely access to advanced therapies and—more importantly—the expertise of an intensivist for those patients who would benefit most. As indicated earlier, quantifying the added benefit of rescue therapies such as ECMO remains a pivotal question.

In the 2009 pandemic, the nation's intensive care capacity was not overwhelmed, although some individual hospitals

nearly reached capacity for a period of time. If many more patients had been referred for specialized care, it is possible that all the US tertiary ICU capacity could have been exceeded during the height of the autumn wave. In a more severe pandemic, it is likely that there would not have been enough tertiary ICU capacity for all who need it. In such severe pandemics, the allocation of scarce resources including hospital beds, ventilators, and pharmaceuticals might preclude large-scale sophisticated care because a move to crisis or contingency standards of care would occur. However, regionalization might still have a limited role in such situations in unburdening smaller hospitals.

If there were a standing system in use all the time, patients with severe ARDS of varied causes—including severe cases of seasonal influenza as well as those with severe pneumonias such as Legionnaire disease [21] or hantavirus pulmonary syndrome [46]—would benefit.

Currently, such triaging of patients to expert centers sometimes occurs for patients with ARDS, but it is often in a haphazard ad hoc manner in which valuable time is lost. It is precisely during the last hours and days before transfer that much of the deleterious effects of mechanical ventilation may occur as the positive pressure and oxygen concentrations are progressively increased in an attempt to maintain adequate oxygenation. In fact, in recent ECMO studies, the less time spent on conventional ventilation before ECMO, the higher the chances of survival [11]. To minimize the numbers of those transferred too late for maximal benefit, clinical criteria based on early patient parameters could be used to identify mechanically ventilated patients with ARDS in need of transfer. Using scoring systems such as the Murray score used in the CAESAR trial or the criteria developed by ELSO during the 2009 pandemic could provide uniform measures for transfer in much the same way as the Injury Severity Score (ISS) does for patients with trauma (Fig. 1) [22].

An alternate model that could be developed would involve community hospitals partnering with tertiary medical centers to provide remote intensivist consultations via telemedicine, similar to what is done with acute stroke evaluations in hospitals without ready access to a neurologist. In fact, the telemedicine paradigm has moved into the realm of the ICU with the rise of telemedicine ICUs, international consultation, and virtual rounding. In this setting, the tertiary care center intensivist could provide suggestions for care and make a determination of whether the patient would benefit from transfer to the tertiary facility. This method may yield better cost-effectiveness parameters than full regionalization. To this end, the US Department of Homeland Security has funded the Crisis Critical Care Capacity and Trauma project through its National Capital Region Urban Area Security Initiative. The aim of this \$3.6 million project is to augment surge capacity to treat mass casualty incident or medical emergency patients via telemedicine [36,37].

Fig. 2 illustrates a schematic of how such a system might operate.

Points	0	1	2	3	4
P/F ratio (FiO ₂ of 1) in mmHg	>300	225-299	175-224	100-174	<100
CXR quadrants infiltrated	Normal	1	2	3	4
PEEP in cm H ₂ O	≤ 5	6-8	9-11	12-14	≥15
Compliance in ml/cm H ₂ O	≥80	60-79	40-59	20-39	≤19

Fig. 1 Murray score.

This system also has the potential to advance research into ARDS by cohorting patients at specific centers in which care can be more protocol driven and clinical research trials of novel therapies can be carried out. During the 2009 pandemic, one such system, the International Forum for Acute Care Trialists H1N1 Research Collaborative, was developed and used to facilitate research [23]. ARDSNet, a clinical network created by the National Institutes of Health's National Heart, Lung, and Blood Institute, is another example that has been a primary driver of research into ARDS treatments.

Lastly, if ECMO becomes a part of this system, economies of scale with ECMO costs could be realized with regionalization.

6. What is needed to realize such a system

To realize the potential benefits associated with the regionalization of care for severe ARDS, there are a number

of financial, regulatory, and practical issues that would have to be addressed. This approach might result in a new standard of care for some patients with ARDS. However, the proposed model is not without precedent. Comparable systems have been developed for other acute diseases including stroke, trauma, and acute myocardial infarction (ST elevation) in which treatment at a specialty center has been shown to decrease morbidity and mortality. Accreditation, the support of professional societies, and the involvement of third-party payers are essential to the success of this proposed system.

Recognizing that there are limitations to comparison of a system for transferring neonates to referral centers to a system for regionalization of adult ARDS, the neonatal intensive care system provides the best evidence that such a system is possible and could, potentially, yield better patient outcomes [39]. Summarizing and combining the data from the neonatal experience, a 2008 Cochrane Review on the cost-effectiveness of using transfer to referral centers for neonatal respiratory distress syndrome yielded a relative risk of mortality of 0.44 and concluded that the neonatal system of transfer is cost-effective [32].

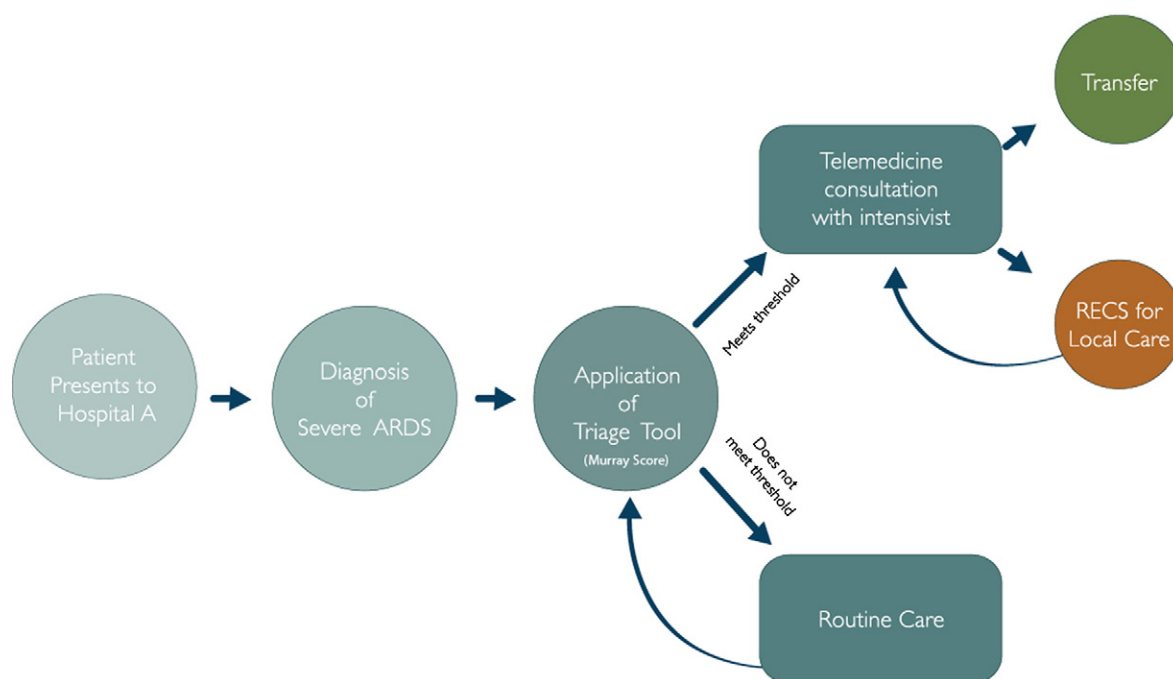


Fig. 2 Conceptual patient flow diagram.

Analysis of conditions such as stroke, myocardial infarction, and trauma yields similar results [33–35] favoring transfer to facilities capable of providing expert care.

However, an often-raised objection concerns the fact that irrefutable evidence of the benefit of transferring adult patients with severe ARDS to referral centers does not yet exist. Although the CESAR trial provided some evidence for this approach, its single-center nature limits its full generalizability. Additional trials are still needed to develop consensus evidence-based criteria. A pilot project using referral centers that have existing relationships with satellite community hospitals may be one such avenue to generate suitable data.

7. Joint commission certification

The Joint Commission could facilitate the move toward regionalization of care by implementing a certification process for the designation of centers of excellence for ARDS as they currently do for various conditions including stroke. The Joint Commission has promulgated criteria for pneumonia—a frequent pathway to severe ARDS—since 2001; however, criteria are limited to only stipulating certain antimicrobial therapy and patient culture specimen benchmarks. Criteria for certification of severe ARDS centers would involve assessing the volume of patients cared for at such centers, the resources available (eg, 24-hour intensivists staffing), and metrics to measure performance. Intensive care unit designation levels based on capabilities, as outlined by the American College of Critical Care Medicine, could serve as a blueprint [24].

8. Third-party payer interest

Another force that could speed the implementation of an ARDS center paradigm is a preference by third-party payers. Acknowledgment by insurers of the benefits of care received at ARDS centers in terms of mortality, hospital length of stay, and ICU length of stay would provide financial incentives for regionalization and, possibly, higher reimbursement rates for hospitals who meet ARDS center criteria. During the 2009 pandemic, a large medical center in California established an ad hoc ALI center with a major insurer (C. Hoopes, personal communication, January 2012).

9. Professional societies

The support of the relevant professional societies (American Thoracic Society, American College of Chest Physicians, American Association of Critical Care Nurses, and the Society of Critical Care Medicine) could also help

bring this concept to fruition. Indeed, during the development of stroke centers, the American Heart Association played a major role and the American College of Surgeons helped organize and now designates trauma centers.

Because members of the aforementioned societies represent a large proportion of ICU physicians from community and academic settings, the support of these societies will likely depend on the prevailing attitudes of their members and cannot be expected to be a foregone conclusion [28]. Community physicians may perceive the development of such a system as a threat to their practices. However, these organizations have already collaborated in the 2005 PrOMIS conference in which one of the consensus solutions to the problems of critical care delivery in the United States was as follows: “regionalizing the adult critical care system into ‘tiers’ defined by explicit triage criteria and professional competencies [29].” In addition, a survey of more than 500 intensivist physicians revealed that a majority believed that regionalization would improve outcomes and efficiency [40].

10. Hurdles to regionalization

Before such a system can become fully operational, several hurdles must be cleared. In addition to the support of third-party payers, the Joint Commission, and professional societies, the biggest barrier may be educating health care providers about the potential benefits of such a system. In addition, there may be concerns regarding potential loss of revenue from physicians and hospitals that transfer patients outside their facility. However, the patients in question are often ultimately transferred to tertiary centers but perhaps too late to benefit fully [43]. Also, transport of potentially unstable patients will need to be optimized to avoid deterioration of condition during transit and minimize the pull on the resources of tertiary care center teams, which may be called on to retrieve patients [31]. Indeed, if clinical deterioration during transportation occurs to a large degree or large demands on resources are required, the potential benefits of transfer may evaporate. Overall, as implied by Kahn et al [38], a paradigm shift in which critical illness—which would include severe ARDS—is considered as analogous to a severe multisystem trauma is needed.

It is unclear how capacity would match demand. It is likely that more adult severe ARDS centers would be needed to accommodate the increased patient population if transfer to an ARDS center were widely accepted. Indeed, ECMO machinery, oscillating ventilators, and even ordinary ventilators are scarce when viewed from a nationwide perspective. Cost-benefit calculations of such an intervention in the setting of pandemics would need development. In addition, the financial incentives that may accrue with Joint Commission certification and third-party payer policies might entice more hospitals to develop their own centers

capable of handling severe patients with ARDS. Professional society and Joint Commission certification would ensure that newly created centers meet specific performance measures. Also, ELSO, through its training courses, could provide assistance to hospitals embarking on ECMO and could provide further certification of centers that meet specific benchmarks. Important consideration must also be given to the potential loss of expertise that may occur in smaller hospitals if such a system was undertaken.

Another hurdle to be considered is the ability of referral hospitals to mobilize staff to retrieve patients from outlying facilities, especially during a pandemic in which staffing may already be constrained.

11. A day-to-day system

The current system for treating patients with ARDS could be improved if the latest research guided all care, especially research that supports the benefit of treatment in a high-volume centers. A formalized network of ARDS centers is a means to fully capture the value of advances in patient management. This system, which has the capacity to save lives during a pandemic, should unequivocally be part of local, state, and regional emergency preparedness planning but, to completely realize its value, should operate on a day-to-day basis.

12. Necessary next steps

To further explore the feasibility, benefits, and concerns regarding a system such as proposed in this study, several steps are necessary to develop consensus and refine the proposal. Among those steps are the formation of an expert group consisting of intensivists, emergency medicine physicians, hospital administrators, accreditation agencies, third-party payers, and representatives of aeromedical and ground patient transportation entities. The focus of such a group would be to systematically develop a checklist of evidence-based practices that can be used to distinguish expert ARDS centers. Using such criteria, pilot/demonstration projects could ensue [39]. This consensus might influence third-party payers, accreditation agencies, and professional societies to fully support this initiative and potentially improve the care of the sickest patients with ARDS in both pandemics and in daily care.

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