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Preparing for the Sickest Patients With 2009 Influenza A(H1N1)

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DESPITE AN ENORMOUS GLOBAL INVESTMENT IN PREparing for the reemergence of 2009 influenza A(H1N1), preparations proceeded largely without empirical data about the nature and severity of disease. This paucity of data is particularly problematic for clinicians in intensive care units (ICUs), who will shoulder a heavy burden for the clinical response to H1N1. In this issue of *JAMA*, 3 reports provide data that begin to fill this empirical void.

Domínguez-Cherit and colleagues¹ conducted an observational study of 58 patients admitted to 6 ICUs in Mexico City with H1N1-related disease during the initial outbreak in spring 2009. Kumar and colleagues² conducted a similar study of 168 critically ill patients in 38 Canadian ICUs. There were striking similarities in the main findings. Patients tended to be relatively healthy adolescents and young adults who developed a brief prodromal illness followed by rapidly progressive respiratory failure. Shock and multisystem organ failure were common. Hypoxemia was prolonged and severe, requiring on average 12 days of mechanical ventilation and frequent use of rescue therapies such as high-frequency oscillatory ventilation, prone positioning, neuromuscular blockade, and inhaled nitric oxide. The influenza outbreak lasted about 3 months in both countries, but the peak lasted just a few weeks, during which time hospitals struggled to accommodate the increased patient load, with 4 Mexican patients dying while awaiting ICU beds. Notably, the Mexican cohort incurred a mortality rate twice as high as that in Canada. In contrast to the high rates of health care worker infections during severe acute respiratory syndrome (SARS) outbreaks,³ there were no documented cases of nosocomial transmission in either series.

The third article, by Davies and colleagues,⁴ is based on data from all centers providing extracorporeal membrane oxygenation (ECMO) for H1N1-related disease in Australia and New Zealand during the 2009 Southern hemisphere winter. The cases were typically young adults with little underlying comorbid disease who developed severe hypoxemia and multisystem organ failure. The median dura-

tion of ECMO support was 10 days, and the case-fatality rate was 21%.

In aggregate, these studies represent important efforts within the intensive care medicine and clinical research communities to rapidly gather, analyze, and disseminate data in response to a new public health threat. It is remarkable to have any data so early in the course of the influenza pandemic, let alone the systematically collected data presented in these reports. Investigators achieved this by using existing clinical research networks and standardized data collection forms developed after the 2003 SARS outbreak. This approach is a model for the future.

Nonetheless, each of these studies has substantial epidemiological limitations. As with all diseases that manifest with a range of symptoms and severity, it is difficult to ascertain the incidence of H1N1 infection in the population and hence the true proportion of affected patients who require hospitalization, ICU admission, or rescue therapies such as ECMO. It is also difficult to infer benefits of certain therapeutic maneuvers because of the potential for selection bias and residual confounding related to differences between groups that did and did not receive treatment. Although the use of standardized case report forms increases the ability to compare results within and across studies, baseline differences in usual care confound causal inferences. This is particularly relevant when trying to reconcile the marked differences in mortality between patients in Mexico and Canada. Much of the value of these reports lies in the extent to which they will help predict the burden of the H1N1 pandemic. However, the ability of the influenza virus to mutate raises questions about whether the virus that will emerge this fall will produce similar rates and severity of clinical infection.

Despite these limitations, these studies^{1,2,4} provide important signals about what clinicians and hospitals may confront in the coming months. H1N1 can produce a rapidly progressive respiratory failure that is refractory to conventional mechanical ventilation, often in young, healthy patients—a group who are not currently a priority group for H1N1 vaccination.⁵ The rapid onset of refractory hypoxemia, together with multisystem organ failure and hypo-

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tion, suggests that clinical outcomes will depend on clinicians' ability to apply sophisticated mechanical ventilatory support and adjunct therapies. Clinicians and hospitals should take note that the rescue therapies used in these studies have the potential to cause harm if not implemented in a coordinated manner. Many US hospitals may not have adequate numbers of physicians with this expertise, or staffing structures to facilitate timely treatment at any time of day or night.

How then might hospitals within a given region respond to the unique needs of the sickest patients with H1N1? One possibility is regionalization of care for patients with advanced respiratory failure. This would allow a few centers to accumulate experience managing the sickest patients, while preserving the resources at outlying hospitals for other patients. Strengths of this approach are the possibility for improved outcomes due to accumulated experience and the potential for streamlined conduct of clinical trials of promising treatments.⁶ A second possibility is the development of telemedicine consultation for clinicians at outlying hospitals who may benefit from expert clinical advice for such tenuous patients. Demonstration projects are ongoing for telemedicine during a public health emergency.⁷ A third possibility is for hospitals to make temporary staffing changes to ensure the continuous presence of clinicians competent to handle these cases. This approach lacks some of the potential benefits of regionalization and may be infeasible because of foreseeable workforce shortages during a severe influenza outbreak.

The case series by Davies and colleagues⁴ raises a particularly critical question: will the use of ECMO decrease mortality in patients with H1N1 who have refractory respiratory failure? Of course, causal inferences should not be drawn from an uncontrolled case series. In theory, however, if ECMO were only initiated in patients who were judged to be certain (or nearly certain) to die without it, a substantial portion of the observed survival may plausibly be attributed to treatment with ECMO. However, there are insufficient details about inclusion and exclusion criteria to conclude that ECMO use was restricted in this way. Recent data suggest that patients who might be considered for ECMO often may survive without it.⁸ Nonetheless, based on the data presented, it seems likely that the mortality rate without ECMO would have been higher than the observed 21%. A final caution about generalizability of the high survival rate observed in this study: not all patients who died from H1N1-related illness were offered ECMO. It is therefore likely that the outcomes were in part due to careful selection of patients.

The large proportion of critically ill patients with H1N1 who survived is an important reminder that the medical response to a respiratory pandemic is very different today than it was for the 1918 influenza pandemic. The widespread availability of antibiotics, antiviral agents, vasopressors, and mechanical ventilation makes it possible to save many patients who would not have survived in 1918.⁹ With this potential comes an obligation for hospitals and public health systems to col-

laboratively develop strategies to ensure that, if there is a resurgence of 2009 influenza A(H1N1), the benefits of intensive care medicine can be offered to the maximum number of patients. Although guidelines and recommendations exist for augmenting hospital surge capacity, their implementation in individual hospitals is far from complete. The investigators from both Mexico and Canada noted that the health care systems struggled to meet the demands created by the increased patient volume, a sobering observation given that the absolute number of excess ICU admissions was modest.

Hospitals must develop explicit policies to equitably determine who will and will not receive life support should absolute scarcity occur. The controversy that erupted around triage decisions during Hurricane Katrina highlights the importance of advance planning and clear guidelines.¹⁰ Several groups have provided recommendations for allocating scarce therapies during the influenza pandemic.¹¹⁻¹³ Any deaths from 2009 influenza A(H1N1) will be regrettable, but those that result from insufficient planning and inadequate preparation will be especially tragic.

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