October 2009

Critical Care Rounds

Quarterly Evidence-based Reviews on Current Topics in Critical Care Medicine by leading Canadian Content Experts

Critical Illness Due to Influenza A 2009 H1N1

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Baseline Seasonal Influenza-Related Health and Economic Burden

Influenza viruses kill hundreds of thousands of people worldwide each year and cost society many billions of dollars in morbidity and lost productivity (1). Based on the 2003 US influenza experience, there was an estimated 610,660 life-years lost, 3.1 million hospital days, 31.4 million outpatient visits and $10.4 billion in direct medical costs, $16.3 billion in projected lost earnings and an estimated total cost burden (including lost-life years) amounting to $87.1 billion (1). This is the fall-out from a usual influenza season.

Influenza viruses kill hundreds of thousands of people worldwide each year and cost society many billions of dollars in morbidity and lost productivity (1). Based on the 2003 US influenza experience, there was an estimated 610,660 life-years lost, 3.1 million hospital days, 31.4 million outpatient visits and $10.4 billion in direct medical costs, $16.3 billion in projected lost earnings and an estimated total cost burden (including lost-life years) amounting to $87.1 billion (1). This is the fall-out from a usual influenza season.

Classical influenza in adults comprises a 4-5 day period of fever, chills, upper-respiratory-tract symptoms, headache, muscle pain, and weakness.

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Acknowledgements: Canadian Institutes of Health Research; Public Health Agency of Canada; John Granton – Chair, Canadian Critical Care Society; John Marshall – Chair, Canadian Critical Care Trials Group and Margaret Herridge – Editor, Critical Care Rounds

Severe complications and death can occur, especially in infants, the elderly, and individuals with chronic medical conditions. Among the most severe complications are pneumonia and secondary bacterial infection leading to respiratory failure (2, 3). Influenza can also cause central nervous system, cardiac, renal and hepatic complications (4, 5). Underlying pulmonary disease is a frequent risk factor, occurring in 18% of patients, most commonly asthma (7%), followed by neurologic disease (12%), hemato-oncologic (9.9%) and cardiac conditions (4.6%) (6, 7). However, approximately half of those hospitalized (rates ranging from 1-5/1000) for influenza are otherwise healthy (2,3, 6-10). In the absence of a pandemic, 11-19% of patients hospitalized with laboratory-confirmed influenza require treatment in the intensive care unit (ICU) (6, 7, 9, 11). The mean duration of mechanical ventilation is approximately 5 days; the sickest patients require treatment with advanced oxygenation techniques such as high-frequency oscillatory ventilation (HFO), extra-corporeal membrane oxygenation (ECMO), prone positioning and nitric oxide. These patients have an attendant increase in length of stay, duration of ventilation and mortality (6, 7, 9, 11).

Between 50-100 million people died during the 1918 pandemic. Death followed from aggressive secondary bronchopneumonia, influenza-related lung disease and associated cyanosis and cardiac collapse (12). During the 1918 pandemic, there was an unexplained excess influenza mortality in persons 20–40 years of age. This mortality increase may have been due to limited native immunity and / or a vigorous immune response directed against the virus in healthy young persons (12). Today the mortality of the 1918 pandemic would almost certainly be reduced because of the availability of ICUs, antibiotics, and antiviral medications – innovations of the mid-twentieth century; the cost will be a dramatic increase in critical care admissions and length of stay, assuming that this capacity is available (13). Long-stay ICU patients have significantly higher critical care and hospital mortality rates compared to short-stay patients, occupy a disproportionate number of critical care bed-days (14, 15), and consume even greater resources (16, 17).

Influenza Viruses – A Primer

Influenza, is caused by RNA viruses of the family Orthomyxoviridae, that affects birds and mammals, and include three genuses, influenzavirus A, B and C (18). Occasionally, viruses can be transmitted to other species, cause outbreaks in animals or give rise to disease in human pandemics. Influenza A virus is typically the most virulent and leads to the most severe disease. Based upon the antibody response to two proteins on the outside of viral particles, Hemagglutinin (HA) and neuraminidase (NA), influenza A is subdivided into different serotypes including: H1N1 (responsible for Spanish flu in 1918, in addition to the 2009 flu pandemic); H2N2 (Asian Flu of 1957); H3N2 (Hong Kong Flu of 1968); H5N1 (often sited as the most recent pandemic threat), and number of others currently less relevant to humans (H7N7, H1N2, H9N2, H7N2, H7N3, H10N7). The two other forms of influenza include B (which almost exclusively infects humans but is less common), and C (affecting humans, dogs and pigs) which only rarely causes severe illness and epidemics).

Influenza is usually transmitted in aerosols by coughing or sneezing, but can be transmitted through bird droppings, saliva, nasal secretions, faeces and blood, or contact with contaminated surfaces. Influenza spreads globally by seasonal epidemics, resulting in hundreds of thousands of deaths annually, and when a new strain of the virus arises from genetic reassortments of flu viruses from human, avian or swine hosts, more virulent strains can result in millions of deaths from pandemic spread. In the 20th century there

were 3 pandemics (1918, 1957 and 1968) which killed tens of millions of people. The 2009 H1N1is derived from a triple recombination of human, avian and swine influenza viruses (19). Most older adults have substantial immunity to H1N1 variants that have circulated during the past century; the early epidemiology of this virus indicates that there may be partial protection from multiple previous influenza infections, despite this being a newly identified virus.

Influenza A 2009 H1N1-Related Epidemiology

Since March 2009, influenza A 2009 H1N1 has spread from the Southwestern US and Mexico to virtually all countries of the world. By September 27, 2009, there were over 340,000 cases with 4100 deaths worldwide (20-22). The WHO has issued the first Phase 6 Pandemic Alert of the century, anticipating substantial influenza transmission and related disease. Over the period of June-September 2009, there have been dramatic spikes in H1N1-related disease in Australia-New Zealand and South American nations that breach the capacity for care in some jurisdictions. In Australian provinces, approximately 5% of the population developed H1N1-related illness, 0.3% of infected patients were hospitalized, and 20% of hospitalized patients required ICU care (23), very similar to the proportions reported by the Public Health Agency of Canada. As the Northern Hemisphere countries approach their influenza season, we anticipate high rates of influenza and 2009 H1N1-related critical illness.

Influenza A 2009 H1N1-Related Critical Illness

Among 168 critically ill Canadian patients with influenza A 2009 H1N1, the mean age has been 32 years with a possible predilection for more severe disease in women (67% of patients) (24). Nosocomial transmission was the mechanism of acquisition in approximately 10% of patients, but none of these patients were health care workers. One or more comorbidities was observed in nearly all patients, most commonly chronic lung disease such as asthma, chronic obstructive pulmonary disease, bronchopulmonary dysplasia or others) (41%), obesity (33%, mean body mass index of 34.6 kg/m^2), hypertension (24%), and a history of smoking (23%), and diabetes (21%). Serious comorbid illness was observed in only 30% of patients. Notably, Aboriginal Canadians have thus far been over-represented (26% of patients).

The most common specific symptoms have included fever and respiratory symptoms in greater than 90% of patients, and less commonly weakness and myalgias. Several severe clinical syndromes associated with influenza A 2009 H1N1 infection may be seen, including:

- rapidly progressive diffuse pneumonitis associated with severe, refractory hypoxemia, in relatively healthy teens or adults;
- decompensation of chronic underlying disease in those patients with serious comorbidities including congestive heart failure, chronic renal failure, end-stage liver disease, poorly controlled diabetes, or immune compromise;
- acute and prolonged exacerbation of chronic obstructive pulmonary disease and asthma in those with pre-existing disease;
- bacterial pneumonia (frequently with gram positive pathogens including *S. pneumoniae, S. aureus* and Group A Streptococci) and superinfection on a background of mild or severe influenza A 2009 H1N1 infection;
- bronchiolitis and croup in infants and young children which may frequently require hospitalization but not ICU care.

The signature clinical syndrome requiring ICU care among all age groups appears to be the diffuse bilateral, four quadrant pneumonitis that can be rapidly progressive. This syndrome has been seen in over 80% of ICU admissions to date in Canada and has frequently required advanced

ventilatory/oxygenation modalities (high frequency oscillatory ventilation (HFOV), inhaled nitric oxide and/or extracorporeal membrane oxygenation (ECMO) therapy) (24).

Canadian patients who subsequently developed critical illness have generally presented to hospital within 4 days of symptom onset, and required ICU admission within 1 day of hospital presentation for bilateral pulmonary infiltrates and hypoxic respiratory failure. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score was 20. Notable laboratory findings have included elevated creatine kinase levels and normal white blood cell counts. Concomitant presenting conditions included possible bacterial pneumonia (32.1%), hypotension requiring vasopressors (13.7%), and asthma or chronic obstructive pulmonary disease exacerbation (13.7%).

Over 80% of patients with H1N1-related acute lung injury received mechanical ventilation, with very few patients sustained with non-invasive ventilation. Oxygenation support included high concentrations of inspired oxygen (mean admission PaO_2/FiO_2 147 mmHg), positive end-expiratory pressure, frequent use of HFOV (12%), nitric oxide (14%), neuromuscular blockade (30%), prone ventilation (5%) and occasional extra-corporeal membrane oxygenation (7%). Medical therapies included neuraminidase inhibitors (90.5%); antibiotics (98.8%) and despite uncertain efficacy, corticosteroids (50.6%).

Secondary bacterial pneumonia following ICU admission was found in 24% of cases, most commonly due to *Staphylococcus aureus* and *Streptococcus pneumoniae.* Overall mortality among critically ill patients at 90 days was 17.3%. The median duration of ventilation was 12 days. The most common cause of death was severe acute respiratory distress syndrome and hypoxemia, complications thereof, secondary infection, sepsis or multiorgan dysfunction syndrome.

Among critically ill Canadian children, the median age was 5.0 years (range 1 month to 17 years), 54.4% were female and the mean PRISM III score was 9. One or more chronic co-morbid illnesses were observed in 70.2% of patients: lung disease (44%); neurological diseases (19%); immune suppression or immunodeficiency (16%); history of prematurity (9%) and congenital heart disease (7%). Two patients were pregnant adolescents and Aboriginal Canadians comprised 25% of the children. Mechanical ventilation was used in 68% of children admitted to ICU and the median duration of ventilation was 6 days (range 0 to 67). Four children died.

Clinical and Laboratory Based Diagnosis

Significant difficulties with definitive diagnosis exist and such difficulties may be aggravated during the anticipated Fall 2009 epidemic wave. Laboratories may face technology limitations and an increase in testing demand for all sectors, during a period when their own staffing may be vulnerable. The initial diagnosis and trigger for initiation of antiviral therapy must be presumptive.

Fever and respiratory symptoms have been present in almost all patients who have progressed to critical illness. However shortness of breath, a symptom that is not typical of uncomplicated influenza virus infection is likely suggestive of severe disease. Other clinical signs noted in patients with severe disease have included hemoptysis, frothy pink sputum and purulent sputum with diffuse lung crackles. Where possible, percutaneous oximetric assessment of oxygenation and / or arterial blood gas evaluation of PO_2 should be performed. Relative hypoxia should trigger further assessment including a chest radiograph. Laboratory findings typically found at presentation with severe disease include normal

or low normal leukocyte counts and elevated creatine kinase (24, 25).

Early laboratory diagnosis of 2009 H1N1 infection ideally requires Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) methodology. Immunofluorescent techniques and enzyme-linked immunoassays of clinical specimens may lack diagnostic sensitivity (26, 27). Viral cultures require up to 1 week for processing. While RT-PCR is the preferred definitive diagnostic technique and has very high sensitivity under ideal circumstances, several Canadian and international outbreak sites have reported imperfect sensitivity of standard nasopharyngeal swab RT-PCR testing in severe cases. These reports have been coupled with others suggesting that tracheal aspirates in intubated patients may increase the diagnostic yield, as may repeat testing within 48-72 hours.

Supportive Care

Almost all patients with severe 2009 H1N1infection in ICU will have deficits in oxygenation and subsequently ventilation (24, 25). A subset have also had shock and renal failure which may have occurred in part as a consequence of efforts to optimize oxygenation though diuresis coupled with high intrathoracic pressures and limited venous return (24, 25). Other important but less frequently seen disorders at presentation may include encephalitis (with or without obtundation or seizure activity) (28-32), cardiac injury (myocarditis, pericarditis, conduction defects)(33-36) and rhabdomyolysis (37-40.

Most elements of supportive care for patients with severe 2009 H1N1 infection are similar to other critically ill patients with ARDS: supportive care for severe hypoxemia in patients with diffuse pulmonary disease and a prolonged duration of oxygenation and ventilation assistance required in such patients (24, 25). A primary difference will be the age of patients (relatively young), and an expectation of much greater numbers than we would experience in a usual influenza season.

One consistent observation among those who have become critically ill is that of rapidly progressive pneumonitis following presentation and a requirement for mechanical ventilation within 24 hours. Patients may display a relative insensitivity to usual measures of oxygenation assistance with positive end-expiratory pressure (PEEP). Controlled ventilation, with attention to a lung protective strategy (41), in combination with appropriate sedation and judicious use of neuromuscular blockade has been commonly used. The severity of hypoxemia and need for patient-ventilator synchrony, coupled with disease in young previously healthy patients, may translate to a greater than usual amount of sedating medications being used. Avoidance of volume overload (and judicious diuresis) may also be associated with reduced duration of ventilation and length of stay in ICU for most patients with ARDS and this strategy should be attempted for patients with H1N1 (42). Other means of oxygenation assistance that have not been shown to improve mortality in other forms of ARDS, but may improve oxygenation for individual patients have included prone positioning (which can be difficult to perform due to the severity of illness coupled with obesity in many patients), and inhaled nitric oxide (43, 44). HFOV is currently being evaluated as a rescue therapy for patients with severe ARDS in randomized controlled trials in many jurisdictions (45) and has been frequently used among patients with H1N1-related refractory hypoxemia. ECMO is an uncommonly used modality of oxygenation assistance in non-transplantation associated acute lung injury in adults. However, a recent study has shown that transfer to a centre experienced with the use of ECMO is associated with improved disability-free survival among patients with ARDS and severe hypoxia (46). Clinicians in Australia similarly recommend consideration of ECMO for recalcitrant H1N1(47) but Canadian experience with ECMO for H1N1-related ARDS

is minimal. If patients are unable to be supported in their current environment and transfer to another center with additional modalities (e.g. HFO, ECMO) is considered, consultation with centres experienced with such modalities in order to determine whether patients are likely to benefit, should occur before the patient is too unstable for transfer.

Antiviral Therapy

Because emerging surveillance evidence suggests that the occurrence and severity of life-threatening influenza A 2009 H1N1 infection may be mitigated through early initiation of antiviral therapy (24, 25), initial treatment decisions should be based on clinical presentation and epidemiological data and should not be delayed pending laboratory confirmation. Although this will result in at least some patients being inappropriately treated with anti-viral therapy, this is preferable to having patients with progressive or severe H1N1 infection untreated pending laboratory confirmation.

Various influenza strains are currently circulating throughout the world. However, it is expected that 2009 H1N1 will substantially if not almost fully replace the seasonal strain as the dominant pathogen during the upcoming influenza season. The 2009 H1N1 variant is resistant to amantidine but sensitive to neuraminidase inhibitors, including oseltamivir and zanamavir (48). At this time, only an oral form of oseltamivir and an inhaled form of zanamavir are available for use.

Published data on oseltamivir and zanamavir and 2009 H1N1 infection is very limited. Trials with sensitive seasonal influenza strains have suggested that initiation of antiviral therapy within 48 hours of onset of symptoms of influenza is associated with a 1-day or greater reduction in duration of symptoms in ambulatory patients (49-51). Data also suggests that oseltamivir therapy may reduce the risk of secondary bacterial superinfection (52). Recent data suggests that early therapy of severe influenza A 2009 H1N1 infections requiring ICU support with neuraminidase inhibitors yields improved outcomes (53, 25).

Little data is available regarding the optimal dose or duration of therapy. Several studies have suggested that severe influenza infections including severe 2009 H1N1 infection may represent a systemic in addition to a pulmonary infection (54-56) which would favor the use of a systemic rather than inhaled antiviral agent. A major concern has been the adequacy of gastrointestinal absorption of oseltamivir among the critically ill who may frequently exhibit significant disruptions of bowel function including ileus. However, published studies(57) and unpublished research communications (courtesy, A Kumar) suggest adequacy of bowel absorption with blood levels comparable to those found in ambulatory patients receiving the same dose. Available evidence suggests that an oseltamivir dose of 75 mg BID is appropriate; higher doses may be considered given limited drug related potential for toxicity, but are not specifically recommended.

Viral shedding has been shown to be prolonged in hospitalized patients with seasonal influenza (Lee CID) and in 2009 H1N1 infections(58, 59). In one study, approximately one-third of patients continued to shed live virus at least 1-week after symptom onset (59). In another, 47% of patients continued to shed virus for 7 days or more; 8% for greater than 10 days following symptom onset, despite therapy with oseltamivir (58). Thus, durations of neuraminidase inhibitor therapy longer than 5 days may be appropriate and many jurisdictions are currently recommending therapy for 10 days for H1N1-related critical illness.

Adjunctive Pharmacologic Therapy

Several potential adjunctive immunomodulatory or antiviral therapies for treatment of severe

influenza exist. The most well-developed may be convalescent serum/plasma or hyperimmune globulin derived from patients who have experienced 2009 H1N1 infection with full recovery. A series of studies were performed using convalescent plasma/serum during the 1918 outbreak. These studies have recently been assessed in a meta-analysis showing that early, but not late, administration of such products may be associated with a significant survival benefit (60). In addition, several short reports and case series have suggested the possibility that similar therapy may be of use in severe influenza A/H5N1 infection(61, 62).

Ribavirin and interferon-alpha are both non-specific antiviral agents with approved indications for certain human viral infections. Inhaled ribavirin is available for use for treatment for Respiratory Syncytial Virus infection causing bronchiolitis in infants less than 1 year of age (63). Various forms of interferon-alpha have been used in the treatment of chronic hepatitis B and C infection (64,65). Both demonstrate evidence of antiviral activity for influenza virus in-vitro and/or in animal studies. Interferon-α has shown some potential efficacy in one human study of Severe Acute Respiratory Syndrome (SARS) (66). However, there is only anecdotal experience with H1N1-related illness.

High dose corticosteroid therapy has been advocated for a variety of infectious and inflammatory conditions. Corticosteroids have been useful as adjunctive therapy to suppress inflammatory responses in certain serious infections including bacterial meningitis (67) and *Pneumocystis jirovici* pneumonia (68). However, they have been shown to be detrimental in other infections, particularly acute viral hepatitis (69). Their role in ARDS is controversial (70). In the most recent large multicenter trials among patients with ARDS, methylprednisolone administered after 7 days of lung injury was associated with a reduced duration of ventilation and ICU stay but no change in mortality (71). Previous studies have indicated that corticosteroids may be associated with increased risk of secondary infections, and neuromuscular disease among patients with ARDS who have received corticosteroids (71, 72).
We advocate that these adjunctive therapies ideally be used in the context of a clinical trial.

Secondary Bacterial Pneumonia

Most data on bacterial superinfection in severe influenza infection derive from studies of previous pandemics. Available evidence suggests the majority of deaths from the 1918 pandemic occurred as a consequence of secondary bacterial infection (73). Similarly, a substantial number of the deaths from the 1957 and 1968 pandemics were caused by bacterial co- or super-infection. The common pathogens in all series have been *S. pneumoniae*, Group A streptococci, *S. aureus* and *Hemophilus influenzae.* In a large Canadian series of progressive or severe 2009 H1N1 infection requiring ICU admission, secondary bacterial pneumonia was seen in 24% of cases with *S. aureus, S. pneumoniae*, Group A streptococci and *E. coli* being the dominant pathogens (24, 25). Given the frequency of secondary bacterial infection, clinicians should have a low threshold for considering antibiotic therapy, including coverage of commonly observed pathogens.

Infection Control in ICU

Patients with suspected influenza should be managed using droplet precautions by healthcare professionals who wear a facial mask. There are different recommendations in different jurisdictions as to which facial mask is optimal. Historically, surgical masks for health care personnel have been the minimal standard of protection. Recent evidence suggests that N95 masks may offer limited to no additional protection in comparison to surgical masks but many jurisdictions advocate for their use when treating patients with influenza (74). Health care workers should also consider appropriate gloves

when the worker is likely to have contact with body fluids or to touch contaminated surfaces, gowns during procedures and patient care activities where clothing might be contaminated, and protective eye wear when providing direct care within one meter of the patient (75). Patients with suspected influenza should be appropriately distanced from other patients, preferably in single patient rooms during the illness phase of hospital admission. If clinical demand exceeds the availability of such quarters, then cohorting of patients with influenza in common areas may be necessary. Patients on droplet Precautions who must be transported outside of the room should wear a mask if tolerated, or when necessary, consideration of an oxygen delivery system that limits spread of aerosol (76).

With respect to infection prevention and control related to mode of ventilatory assistance, there is no overwhelming evidence to promote or deny particular modes. During the SARS outbreak, which was associated with a much greater degree of nosocomial spread than seasonal influenza, there was concern that non-invasive and high frequency oscillatory ventilation may promote excess aerosolization of viral laden particles and place surrounding patients and staff at risk. Limited evidence suggests that the process of endotracheal intubation, especially in an uncontrolled setting, may be associated with increased risk of acquiring infection; however, this risk is mitigated extensively if adequate personal protective equipment is worn (77,78). Patients with H1N1-related ARDS are unlikely to have a quickly reversible lung injury, and prior studies suggest that non-invasive ventilation is unlikely to provide definitive ventilation support and obviate the need for invasive support for these patients (79). This, coupled with the potential risk of increased aerosolization, leads us to recommend against prolonged non-invasive ventilation. Although HFOV may also generate substantial aerosol, this concern may be mitigated by rapid piston shut-down with disconnections and loss of pressure in the circuit. Most HFO circuits can also be equipped with bacterial viral filters and a scavenger system to the exhalation port that further mitigates risk.

Preparing to manage a H1N1 surge and resource allocation

Based upon several experiences during the first wave of H1N1 in both the northern (80,81) and southern (82) hemisphere, as well as recent computer modeling (83), it is likely that most intensive care units will face some degree of surge in demand due to H1N1 this fall or winter. Any plans hospitals develop to respond to H1N1 in the fall should be consistent with their general surge management plans. Several publications provide advice for critical care surge management (84-92) and the Canadian Critical Care Society has recently released recommendations specifically aimed at helping ICUs manage H1N1 this fall (http://www.canadiancriticalcare.org/). Another useful site to find information about preparing for the return of H1N1 is http://www.icu-pandemic.org/. Should shortfalls in essential resources (i.e. ventilators or staff) occur despite all reasonable efforts to surge have been made, then the issue of triage for allocating scarce resources must be considered. Medical protocols for tertiary triage have been developed(88, 93, 94). However, these protocols are new with the first studies evaluating them only recently having been completed and soon to be published in Critical Care [personal communications M. Christian]. Further, the medical protocol is only one component of conducting triage. Many legal and logistical issues remain leaving most provinces unprepared to be able to institute triage ethically or effectively at this time. Thus, while it is important to continue to work on these issues, ideally adequate surge preparations should be made to try and avoid the need for triage. Barring any significant changes in the virus, if hospitals and governments take the necessary steps now, it should be possible to avoid resource shortfalls.

Influenza and H1N1-Research Initiatives

Clinical Studies

The academic critical care community has engaged in H1N1-related research from the first description of illness in the spring of 2009. Authorities from Mexico, the United States and Canada collaborated to describe clinical cases (95, 96) and identify the virus. Critical care physicians in Mexico City contacted colleagues in Canada with experience in SARS-related critical illness to request assistance with outbreak-related education and methods of describing clinical cases to others which lead to the development of a case report form (97) to collect demographic, clinical presentation, comorbidity, organ dysfunction, treatment and outcome information. An observational study received expedited research ethics board review in both countries and the data collection form was then disseminated broadly to critical care societies in Canada, the United States, Australia-New Zealand, the UK and the European Union and posted on academic institutional and critical care society websites by the beginning of May 2009 (98-101). An observational study was then conducted in Mexico and Canada during April-August 2009 which has resulted in dissemination of H1N1-related clinical experience to colleagues across the globe (24, 25). From these initiatives have emerged descriptive studies of children with H1N1, those who received ECMO, translational biology studies on gastrointestinal absorption among others, autopsy studies, and now interventional studies of neuraminidase inhibitor dosing.

Global Critical Care Collaboration

A working group comprised of members from the international critical care community formed the International Forum for Acute Care Trialists (InFACT) to aid with global collaborative research in critical care (101). For the 2009 H1N1 pandemic, the InFACT group has focused upon 4 areas. First, the InFACT web site (www.InFACTGlobal.org) went 'live' in mid-October and provides the critical care community with an international forum for communication and research. Second, InFACT has used the initial CCCTG case report form as a reference for the generation of an international "minimal clinical dataset" through collaboration with members of global critical care societies. This web-entry case report form will allow Canadian centres and hospitals from around the world to contribute patient based data in a manner that can be analyzed in real-time and help inform decision-makers and clinicians during the outbreak. Third, using the web-entry case report form as a clinical information system, InFACT will support large, simple investigator-initiated interventional studies in many countries. Finally, this initiative aims to assist with mechanistic and translational research during the H1N1 pandemic by linking basic scientists with clinicians and clinical data. The impact of the InFACT initiative will only be determined over time, but is an important global critical care attempt to more efficiently and more inclusively improve the care of critically ill patients.

Summary

The 2009 H1N1 influenza A virus that has targeted not only those with chronic medical illness, the very young and old, but also a large segment of the patient population that has previously been afforded relative protection – those who are young, generally healthy, and immune naive. The illness is mild in most, but results in hospitalization and severe ARDS in an important minority. Among those who become critically ill, 20-40% will die, predominantly of severe hypoxic respiratory failure. However, and potentially in part due to the young age of those affected, intensive care with aggressive oxygenation support will allow most people to recover. The volume of patients infected and with

critical illness may place substantial strain on the capacity of the health care system and critical care most specifically. Despite this, the 2009 pandemic has engaged our specialty and highlighted its importance like no other. Thus far, the national and global critical care response has been brisk, collaborative and helpful - not only for this pandemic, but for subsequent challenges in years ahead.

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