Novel Influenza A (H1N1) Surveillance Registry

Co-Principal Investigators:
Todd W. Rice, MD, MSc
Vanderbilt University School of Medicine

B. Taylor Thompson, MD
Massachusetts General Hospital
Harvard Medical School

and

Adrienne G. Randolph, MD, MSc
Harvard Medical School
Children's Hospital Boston
Chair, Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network

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1. Background

In April, reports of patients infected with a novel influenza strain, namely novel influenza A (H1N1) or novel swine-origin influenza virus (S-OIV), began emerging in both Mexico and the Western United States.[1,2] Since April, this virus has spread across the world, infecting patients on every continent except Antarctica. In mid July 2009, a total of 122 countries had reported almost 100,000 cases of novel influenza A (H1N1) virus infection with almost 35,000 cases resulting in 170 deaths in the United States.[3] The World Health Organization increased its level of emergency to pandemic this Summer and recently released a "call to action" to support governments and communities to reduce the impact from the pandemic (H1N1) 2009.[4] The global community expects an exponential growth in the number of infected patients this fall and winter. Reports from the Southern Hemisphere, which is currently experiencing pandemic levels of influenza in its winter months, suggest that the number of patients who contract H1N1 influenza in the United States will increase exponentially and could stress the limits of our healthcare system.

Although only a small proportion of patients infected with novel influenza A (H1N1) require intensive care, it appears that those who do have especially severe disease with profound hypoxemia. They often receive very resource-intensive care, including unproven "rescue therapies".[4-6] These severely ill patients also often suffer from non-pulmonary organ failures, including renal failure requiring dialysis, shock, central nervous system failure with seizures and encephalitis, and hepatic failure. Venous thromboembolic disease may play a larger than expected role in the severity of illness in some of these patients, while others have hemorrhagic pneumonitis.[4] The mortality risk from this strain of influenza, namely novel H1N1, may be higher than more typical influenza strains. Preliminary reports suggest that young, previously healthy individuals, obese patients, and pregnant females may be especially prone to severe infections, critical illness, and worse outcomes.[4-7] However, many of the clinical characteristics of patients who experience severe infections requiring intensive care have not been described in detail, including demographics, risk factors, clinical laboratory manifestations, clinical course, and outcomes.

The Centers for Disease Control has established programs for identifying and monitoring influenza outbreaks in the community. Unfortunately, these programs are largely designed to understand the overall burden of disease and focus largely on outpatients and prevention. While deaths from influenza are monitored, details of the clinical course and resource utilization of fatal influenza cases are not. Programs detailing the intensive care unit (ICU) course or clinical characteristics of critically ill patients are lacking, despite the need for resource utilization planning. The Acute Respiratory Distress Syndrome Network (ARDSNet) is a consortium of academic medical centers and affiliated hospitals across the United States funded by the National Heart Lung and Blood Institute of the National Institutes of Health.[8] The ARDS Network has studied acute lung injury since its inception in 1994 and currently includes 12 core academic medical centers and more than 40 hospitals working on its mission of improving outcomes in patients with acute lung injury and ARDS. The Centers for Disease Control and Department of Health and Human Services asked the ARDS Network to establish a registry of critically ill novel influenza H1N1 because it has been successful conducting multi-center clinical trials and because of its diverse regional representation and established infrastructure. In order to obtain information on children with H1N1, the ARDS Network is partnering with the Pediatric Acute Lung Injury and Sepsis

Investigator's (PALISI) Network. The PALISI Network is a similar consortium of clinical investigators across pediatric intensive care units in the United States and Canada and is supported by voluntary dues paid by each member and affiliated institution. The Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network has studied acute lung injury and sepsis in infants and children since its inception in 2002 and currently includes investigators at 65 pediatric intensive care units across the US and Canada working on its mission of improving outcomes in children with acute lung injury, ARDS and sepsis. A better understanding of the burden of disease, severity of illness, clinical course, and resource utilization is needed to optimize patient care. Furthermore, if the healthcare community is overwhelmed by the numbers and severity of illness of patients with this disease, this information will be vital in making important decisions on how to allocate resources.

2. Rationale and Specific Aims

The demographic characteristics, clinical features, course, and outcomes of severe H1N1 influenza infection requiring intensive care have not been defined rigorously and systematically. While the majority of patients in early reports of critically ill novel influenza A (H1N1) have respiratory involvement, up to 10-20% may present with non-respiratory organ failures, such as shock, seizures, or acute renal failure. The burden of disease and resource utilization of these patients remains largely unknown. The purpose of this prospective surveillance registry is to characterize the demographics, clinical features, outcomes, and resource utilization of patients with H1N1 influenza infection who require intensive care. This purpose will be accomplished through the following five specific aims:

1. To describe the demographics and clinical characteristics of patients with H1N1 who require ICU level care in ARDS Network or PALISI Network hospitals.

2. To describe the incidence of acute respiratory failure in patients with H1N1 influenza infection admitted to participating ICUs. Specifically:

    a. To describe the ventilator needs during the ICU stay of patients with H1N1 cared for in either ARDS Network or PALISI Network hospitals
    b. To describe the incidence of non-invasive ventilation in patients with H1N1 influenza infection cared for in ICUs of ARDS network sites
    c. To describe the incidence of unproven "rescue therapies", such as alternative modes of ventilation (high frequency ventilation, extra-corporeal gas exchange, and prone ventilation), inhaled pulmonary vasodilators, corticosteroids, and neuromuscular blockers used in patients with H1N1 influenza infection and severe respiratory failure

3. To determine the incidence and timing of non-respiratory organ failures, such as renal failure, use of dialysis, use of vasopressors, hepatic failure, and hematologic failure, in patients with H1N1 infection requiring ICU level care in ARDS Network and PALISI Network Sites.

4. To determine outcomes and estimate resource utilization by determining 28-day and 60-day mortality, cause of death, duration of mechanical ventilation, length of dialysis, and ICU and hospital lengths of stay in patients infected with H1N1 influenza who require ICU level care at ARDS Network or PALISI Network hospitals.

5. To compare the endpoints outlined in aims 1-4 for confirmed H1N1 cases with confirmed seasonal influenza A and B infection. Confirmed H1N1 cases will be defined as those identified as having H1N1 with positive rt-PCR testing or viral cultures. Similarly, confirmed seasonal influenza A and B infection will be defined as those patients identified as having influenza A or B by rt-PCR or viral culture or influenza A by screening test with negative H1N1 confirmatory testing (rt-PCR).

3. Animal Studies and Previous Human Studies

There are no pertinent animal studies of H1N1 influenza. Human studies are limited to case reports or case series which report on relatively limited number of patients. These reports suggest that although severe disease requiring critical care is rare among patients with H1N1 infection, the patients who do require ICU care have a rapidly progressive course with high disease severity. Unlike typical influenza, where the extremes of age (i.e. elderly and very young) and those with underlying cardiopulmonary comorbidities are at increased risk of developing severe and potentially fatal infections, young otherwise healthy patients (including children of all ages), obese patients, and pregnant females appear to be at an increased risk for severe disease from the novel influenza A (H1N1) virus.[3,5,6,9]

4. Inclusion/Exclusion Criteria

Confirmed Influenza: A ***confirmed case*** of influenza (any strain) virus infection is defined as a person with an acute illness admitted to an ICU with laboratory confirmed influenza A or B virus infection

Suspected Influenza: A ***suspected case*** of influenza virus infection is defined as a person admitted to the ICU without a positive influenza test but where the clinical team's suspicion for influenza was enough to treat empirically with anti-virals for influenza for the lesser of 5 days or until death. If another diagnosis is found to explain the patient's acute illness (e.g. RSV or *Legionella pneumophila*)) then the person should NOT be considered a suspected case for this registry.

<u>Retrospective Data Collection (approximately 250 Patients)</u>

Inclusion Criteria:

- Admission to an intensive care unit at a participating site with confirmed Novel H1N1 Influenza infection

<u>Prospective Data Collection Patients (Up to 1750 Patients**)**</u>

Inclusion Criteria:

- Confirmed or Suspected Influenza Infection
- Admission to an intensive care unit at a participating site

Exclusion Criteria:

- Influenza-like illness due to non-influenza disease and negative testing for influenza

5. Enrollment/Randomization

There will be no randomization in this surveillance registry. All patients who meet the inclusion criteria and not the exclusion criterion will be enrolled by ARDS Network study personnel. Most patients will be collected prospectively. However, data on approximately 250 patients (~150 adults and ~100 children) will be collected retrospectively. These patients will be patients admitted to the intensive care unit with confirmed influenza infection after April 15, 2009 Since obtaining complete information on every patient with influenza in designated ICUs is vital for accurate estimation of clinical resource utilization, and to avoid biased exclusion of patients without surrogates, we will request a waiver of informed consent to conduct this public health survey and a waiver of authorization for both the prospective and retrospective data collection. During a pandemic and the inevitable shortage of health care workers that results due to illness and absenteeism, it is anticipated that many research personnel will be involved in patient care activities. Thus the time required to contact surrogates will pose an undue burden on these healthcare personnel. Thus this work cannot practicably be conducted with informed consent. The registry procedures are minimal risk in that all data being collected is available in the medical record as part of routine care. A waiver of authorization under HIPAA is needed as the data can not be fully de-identified due to the need to include dates. Dates are needed to fully and accurately track the epidemic and thus serve the National Interest. The data will be held on a server at the Clinical Coordinating Center (CCC) at the Massachusetts General Hospital in Boston. A data use agreement with Massachusetts General Hospital will be made available to all sites requesting it.

6. Registry Procedures

All procedures for this registry pose minimal risk. No samples or specimens will be collected as part of this registry. Data will be collected prospectively from the medical record and transferred electronically to the electronic database, REDCap (Research Electronic Data Capture) (http://www.project-redcap.org/) for storage.[10]

Patients will be enrolled on the day of ICU admission. Baseline demographics, including age, race, gender, ethnicity, height, weight, influenza vaccination status, co-morbidities and admission medications will be collected from the medical record. The presenting clinical features will also be collected, in addition to date of onset of symptoms, dates of admission to the hospital and ICU. APACHE III (or PRISM for children) and Sepsis-related Organ Failure Assessment (SOFA) scores will be calculated for data present in the medical record on enrollment. Baseline lab values for organ function (i.e. renal, hepatic, hematologic, respiratory, and musculoskeletal) will be collected as well as worst value during a patient's hospital stay. Ventilator status will be collected from the medical record. Type and duration of anti-viral therapy during the ICU stay will be recorded. The number of quadrants with infiltrates on chest X-ray will be recorded. Crude outcomes, including survival status, need for ICU care, dialysis, vasopressors, mechanical ventilation, and ECMO (in children only) will be collected weekly in order to have a real-time picture of the clinical course, allowing resource utilization decisions to be modified and adjusted to provide optimal patient care during the pandemic. At ICU discharge, death or day 28, more in-depth outcomes, such as severity of organ dysfunction and bacterial co-infections or nosocomial infections will be collected. The development of additional organ failures, such as myositis, myocarditis, or encephalitis/seizure/delirium will also be collected at this time. Treatments specific for influenza during the ICU course, including administration of antiviral medications or immune

plasma or immunoglobulin will also be collected retrospectively after day28. 60-day follow-up for survival status, lengths of hospital and ICU stay, and duration of mechanical ventilation will be collected for patients who remain hospitalized beyond day 28. In children remaining hospitalized beyond day 60, this information will be collected at day 90. Cause of death will be recorded for all deceased patients and a de-identified autopsy report will be requested.

7. Risks of the Registry

The only research procedures for this registry are collection and transmission of existing clinical data that will be collected solely for non-research purposes. This registry represents minimal risk as defined by the federal regulation 45 CFR 46.110 (F)(5) for expedited IRB review. Loss of confidentiality represents the main risk, and this is minimized through the use of the secure electronic REDCap database. REDCap, housed on servers located at Massachusetts General Hospital, is a secure, web-based application designed to support data capture for research studies and registries. REDCap provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Only Clinical Coordinating Center (CCC) staff at Massachusetts General Hospital for the ARDS Network with appropriate permissions will be allowed to access the database. Data will be automatically sequestered by site so individuals at any institution may see their own site's data, but not data collected at other sites. The REDCap database was developed by the REDCap consortium, comprised of 57 active institutional partners using CTSA, GCRC, and RCMI resources. Current ARDS Network sites that participate in the consortium include: The Cleveland Clinic, Duke University, Johns Hopkins University, The Mayo Clinic, Metrohealth Medical Systems, University of Colorado Denver, University of North Carolina at Chapel Hill, University of Utah, University of Washington, and Vanderbilt University. However, sites do not have to be a member of the consortium to be able to securely login and enter data in a REDCap database. Authorized users can input data from anywhere in the world with secure web authentication and data logging.

Only de-identified data will be included in the database, with the sole exception of dates. Because the REDCap database is housed on servers at Massachusetts General Hospital, they will have access to the actual dates in the database. Due to their access to dates and the fact that dates represent identifiable Private Health Information (PHI) a data use agreement with Massachusetts General Hospital will be made available to all sites requesting it.

Weekly reports will be prepared for the Office of Preparedness and Response and the Center for Disease Control in the United Stated Department of Health and Human Services. Only de-identified data will be released as outlined in the data use agreement between the clinical sites and Massachusetts general Hospital.

8. Waiver of Consent

We propose to conduct this registry with both a waiver of the requirement for informed consent and HIPAA authorization for both the retrospective and prospective data collection. Waiver of consent is appropriate for this registry because the research procedures pose minimal risk to study participants. Moreover, for the registry to be useful, data are needed from every patient at the participating sites who meet the inclusion and exclusion criteria.

Because of sedation and delirium, most patients will not be able to provide informed consent for themselves. For many patients, legally authorized representatives are not available to provide informed consent. Moreover, some family members who could be the legally authorized representatives may be ill with influenza or encouraged not to come to the hospital due to the risks of exposure to themselves and others. Thus, conduct of this study would not be practicable without a waiver. Since spread of this virus can occur from person-to-person via droplets of respiratory secretions, limiting exposure will be an integral part of limiting spread of the disease. As such, the number of people exposed to these patients should be limited to as few as possible, including both family members and registry personnel who are not involved in directly caring for these patients. Mandating consent would increase exposure and possibly worsen spread of the virus. The waiver of authorization is necessary as dates will be collected and thus the database will not be fully de-identified. Dates are necessary to accurately track and describe the epidemic and to serve the public interest.

Any lab test, value, or piece of data that is not part of the medical record will be left as missing in the registry. No tests or data will be required solely for this registry

9. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The main potential adverse event is loss of confidentiality via breach of private health information. Any disclosure of identified health information to unauthorized parties will be reported to the appropriate Institutional Review Board within 5 days of discovery. In addition, the breach will also be evaluated to determine if it also needs to be reported to the local, state, or federal authorities according to respective regulations.

10. Registry Withdrawal/Discontinuation

Since this registry will be collected using waiver of consent, a complete dataset will be collected on all patients.

11. Statistical Considerations

Retrospective data collection patients will be approximately 250 patients (~150 adults and ~100 children) admitted to the ICU with influenza infection beginning April 15, 2009. All prospective patients with confirmed or suspected influenza requiring ICU care at a participating institution from the time of IRB approval through June 30, 2010 will be included in this registry. The proposal is to collect data on a total of 2000 patients; however, the exact sample size remains unknown due to uncertainty about the number of people who will be infected and the percentage of those who will require ICU care. We anticipate the number will range from 30 – 500 patients at each site.

12. Privacy/Confidentiality

Data will be entered into REDCap, an electronic web-based database. REDCap provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to

common statistical packages; and 4) procedures for importing data from external sources. Only research staff with appropriate permissions will be allowed to access the database. Data will be automatically sequestered by site so that individuals at any institution may see their own site's data, but not data collected at other sites. Primary study coordinators will have no access to case report form data views, but will instead have rights to use a single export module designed to enable export of all site data as a limited data set.

13. Follow-up and Record Retention

Data will be collected on patients requiring care in participating hospital ICUs from the time of IRB approval through June 30, 2010. Patients will only be followed to the earlier of hospital discharge, death, or 60 days. There will be no post-discharge follow-up for this registry. Data will be retained for six years after completion of the registry.

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