



H1N1 FLU REGISTRY ON INTENSIVE CARE

Documentation

Scientific Manual

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1. SUMMARY

A new influenza A virus was identified by the United States CDC in April this year in samples from two cases and retrospectively in cases in Mexico. Since then, the disease has spread massively to all continents, causing a number of deaths, and raised the worldwide pandemic alert level to Phase 6. Given the importance of the pandemic and the fundamental role of Intensive Care specialists in the management of these patients, the European Society of Intensive Care Medicine (ESICM) has developed a web-based resource in order to collect information that could inform future planning and management strategies.

This web-site is intricately linked with our own and will be able to be accessed and viewed directly from our home page. It includes a Registry for inclusion of data from critically ill patients with the H1N1 virus, since none exists in Europe regarding specifically the critically ill patient due to the pandemic flu. The web site also includes a resource of documents and National guidelines to help clinicians decide on the best or most appropriate avenues for treatment.

The ESICM H1N1 Flu Registry on Intensive Care is an observational, prospective, multicenter study that will allow us to describe patients' characteristics and management practices in patients with H1N1 flu treated in ICU. This registry aims to describe the epidemiological and demographics characteristics of patients with H1N1 Flu requiring Intensive Care Management.

The H1N1 Flu Registry on Intensive Care project is conducted by the ESICM H1N1 Flu Registry on Intensive Care in cooperation with the ESICM Task Force on ICU Triage for Pandemic Influenza and other disasters and the Working Group on Pneumonia.

The success of the H1N1 Registry research project is strongly dependent upon your participation. Be welcome!

2. INTRODUCTORY NOTE: THE BIRTH OF A PROJECT

On June 11, 2009, the World Health Organization(WHO) signaled that a global pandemic of novel influenza A (H1N1) was underway by raising the worldwide pandemic alert level to Phase 6 This action was a reflection of the spread of the new H1N1 virus, not the severity of illness caused by the virus. At the time, more than 70 countries had reported cases of novel influenza A (H1N1) infection and there were ongoing community level outbreaks of novel H1N1 in many parts of the world.

The proposal for the development of a Registry for H1N1 cases on Intensive Care in Europe based on a web-resource, resulted initially from several discussions between Rui Moreno, Jordi Rello, Andrew Rhodes, Thiago Lisboa and Charles Sprung. Given the importance of the pandemic and the fundamental role of Intensive Care specialists in the management of these patients, a steering group (The ESICM H1N1 Flu Registry on Intensive Care) was created and a web-based resource developed in order to collect information that could inform future planning and management strategies. This web-based resource will provide up to date information regarding the pandemic, with a resource of documents and National Guidelines and contain a registry of H1N1 Flu cases requiring Intensive Care Management in Europe and around the world.

3. BACKGROUND

In recent months, the World has faced a global pandemic of novel Influenza A (H1N1). As of July 6, a total of 122 Countries had reported 94,512 cases of the new Influenza A (H1N1) virus infection, 429 of which were fatal. The spread of the new virus caused the WHO alert level to be raised for the Pandemic to Phase 6, the maximum alert level possible. As more cases were reported, several distinct characteristics were described for the Flu episodes due to H1N1.

Clinical features of an uncomplicated influenza are virtually indistinguishable from other respiratory viral infections. Influenza is characterized by an abrupt onset of headache, high grade fever, chills, dry cough, pharyngeal irritation, myalgia, malaise and anorexia. However, a very common presentation is the adult patient who presents within the first 4 days with acute respiratory syndrome and alveolar opacification involving two or more lobes. Nonetheless, cases of novel H1N1 virus have included rapidly progressive lower respiratory tract disease resulting in respiratory failure, development of Acute Respiratory Distress Syndrome (ARDS) and need for ICU admission. It may occur as a continuum of acute influenza syndrome when caused by the virus alone (primary pneumonia) or by a virus plus bacteria after a delay of a few days (secondary pneumonia). The fulminant primary pneumonia carries a mortality rate in excess of 50% and is uncommon except during pandemics, when immunity to the virus is minimal or absent. It most often occurs in young adults, characterizing a new epidemiological profile that should be studied.

Most of the cases described nowadays are from USA, Canada, Mexico and Argentina. Epidemiological characteristics of these patients include a high rate of hospitalization, with a need for ICU admission of around 25%. Of the hospitalized cases, median age is between 20-30 years and more than 75% are under age 55 years. Several risk factors have been described in small series of cases. Pregnancy, obesity and metabolic disorders, heart disease, asthma or other chronic lung disease are important recognized risk factors for severe presentation of the H1N1 Flu. To recognize higher risk patients might be a key factor for rational use of resources and a better understanding of the processes leading to rapid clinical deterioration and the development of complications.

Further characterization of severe cases of novel Influenza A (H1N1) virus infection is needed to determine the epidemiological profile, to identify higher risk groups, and patients who could benefit more from specific therapies in the Intensive Care setting. With this main aim, we have designed this large prospective, multicenter, observational study to describe the epidemiological and demographics characteristics of patients with H1N1 Flu requiring Intensive Care Management.

4. OBJECTIVES FOR THE ESICM FLU REGISTRY ON INTENSIVE CARE STUDY

The ESICM H1N1 Flu Registry on Intensive Care is an observational, prospective, multicenter study that will allow us to describe patients' characteristics and management practices in patients with H1N1 flu treated in ICU. The main objectives of this project include:

- A) To describe the epidemiological and demographics characteristics of patients with H1N1 Flu requiring Intensive Care Management;
- B) To describe the typical presentation and the natural history of this disease in patients treated with the available drugs;
- C) To know the incidence and severity of patients admitted to Intensive Care setting with H1N1 Flu;
- D) To evaluate clinical variables that could be used to assess prognosis in this group of patients and predict evolution to ARDS and organ dysfunction;
- E) To compare clinical characteristics and therapeutic practices among the several Countries involved in the study;
- F) To evaluate outcomes associated with H1N1 virus infection and the impact of different therapeutic strategies used.

5. METHODS AND STATISTICAL ANALYSIS

5.1. The database and data collection

To develop the project and set up the adequate reference lines, a large multinational, multicentre database was built. The database is accessed online at <http://h1n1registry.com>. The authorization to include patients by providing a username and password is made by the National Coordinator in each Country.

All patients with H1N1 Flu admitted to an ICU will be accepted. A list of the countries that will participate in the H1N1 Flu Registry on Intensive Care study, together with the respective country coordinators, can be found elsewhere (See annex). This list can be eventually subject to changes if other countries decide to integrate the project.

Data should be collected from ICUs for all patients admitted with H1N1 Flu, following the schedule outlined below:

- Each participating ICU will receive a Notification Case Report Form (NCRF) (See annex) for notification of new H1N1 flu case from the National Coordinator in each Country.

- In each participating ICU, NCRF data will be collected for a patient admitted with H1N1 Flu and the NCRF will be sent to the National Coordinator of each Country;

- The National Coordinator should contact CCC to notify a new case in a new center. The CCC will provide a username/password allowing inclusion of the case and full data in an electronic database.

The collection of data will be made using a computerized system, an Electronic Case Report Form (eCRF), based on the web. This web-based registry will be available in <http://h1n1registry.com>.

5.2. Variables

The H1N1 Flu Registry on Intensive Care database was built around a core of data describing the major patient characteristics (chronic health status, severity scores, epidemiological issues, degree of physiologic dysfunction, etc.) known or supposed to influence outcome in H1N1 flu patients. These variables are available in a web-based eCRF. Around this basic information, nine domains were defined:

- Demographic data
- Eligibility criteria
- Chronic comorbidities
- Severity assessment
- Admission Data
- Time Course and Outcomes
- Complications
- Treatment
- Clinical Variables Evolution

5.2.1 Demographic Data

The demographic data include basic characteristics of the patients allowing us to identify specific demographic subgroups who could be at different levels of risk for worse outcomes. It includes:

- Age
- Anthropomorphic data
- Previous Immunization
- Gender
- Race

5.2.2 Eligibility Criteria

Allow to identify cases as definite, probable or suspected and to evaluate the need for intensive care management as major eligibility criteria. All patients identified as definite, probable or suspected H1N1 Flu case admitted to the ICU are eligible for the registry.

5.2.3 Chronic Comorbidities

It includes a list of comorbidities that are or are likely to be associated with prognosis in flu patients.

5.2.4 Severity Assessment

It includes severity assessment tools such as clinical score which could help to stratify severity in flu patients. The main objective of this domain is to provide fundamental information regarding validity of these tools in this specific group of patients.

Scores included are:

- APACHE II Score
- SAPS 3
- Pneumonia Severity Index (PSI)
- CURB-65
- CAP – PIRO
- Charlson Comorbidities Index

5.2.5 Admission Data

It provides important information regarding admission health status of the flu patient and it will allow the analysis of prognostic factors for this population. It includes data on:

- Clinical manifestations and duration
- Medications in use at admission
- Diagnostic techniques used
- Specific findings related to admission
- Cardiac Function

5.2.6 Time Course and Outcomes

This domain gives fundamental information regarding outcomes (mortality, length of stay, residual organ dysfunction). It includes variables describing:

- Time of onset of symptoms
- Hospital and ICU Admission dates and length of stay
- Need and duration of mechanical ventilation (invasive or non-invasive)
- Use of special techniques (e.g. ECMO and Nitric Oxide)
- Persistence of Positive PCR for H1N1
- Death: Date, location and cause
- Residual Organ Dysfunction

5.2.7 Complications

It will collect data on the complications associated with the flu developed during ICU stay. It will allow knowing the epidemiology of such complications and its association with prognosis in these patients. Variables assessed in this domain include:

- Pregnancy Outcome
- Septic Shock – presence and characteristics such as source and documented pathogen
- Pneumonia – presence and pathogen associated
- Neurologic complication such as Guillain-Barré, associated with the H1N1 Influenza Virus
- Record other possible manifestations of the H1N1 virus such as pericarditis, encephalitis or other not described.
- Microbiological data of eventual septic complications in these patients

5.2.8 Treatment

The treatment domain will deal with aspects of management of flu patients in the ICU setting. Inputs required in this domain include:

- Antiviral specific treatment, doses and duration
- IV Antibiotic: Use, agent, doses and duration
- Use of supportive therapy (diuretics, vasopressors, inotropes, hemofiltration or hemodialysis)
- Use of corticosteroids (dosis, duration, agent)

5.2.9 Clinical Variables Evolution

The objective of this domain is to provide a detailed follow-up view of the patient during acute phase of disease in the ICU. It will include daily data in the first 7 days after admission and at the discharge day.

- Daily information on the presence and degree of physiological derangement;
- Daily information on the use of major monitoring and therapeutic devices;

5.3. Data Quality

The data collection software will include plausibility controls. To ensure the maximum quality of the collected data, each variable has to be exactly defined prior to the start of data collection:

- Definitions of each of the variables collected;
- A range of possible values (storage range), encompassing all the possible values for that variable (e.g. for FiO₂, no values lower than 21% or greater than 100% will be

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accepted). The software will not allow the recording of values outside the storage range;

The reliability of data collection will be analysed formally, using K-statistics or intra-class correlation coefficients, as appropriate. The procedure to select the sample to be tested should be defined prior to the beginning of data collection.

5.4. Statistical Analysis

The selection of variables to be collected is based on data published in the literature; all the variables are routinely available. Categorical variables will be described as proportions and will be compared using chi-square or Fisher's exact test. Continuous variable will be described as mean and standard deviation or median and interquartile range depending on the presence of normal distribution. Comparisons in continuous variables will be performed using one-way ANOVA or Mann-Whitney test when appropriate. A logistic regression model will be performed to assess independent association between prognostic factors and outcomes. A two-tailed p value < 0.05 will be used to define statistical significance.

6. ORGANIZATION AND COORDINATION OF THE PROJECT

6.1. Coordination and Administration

The H1N1 Registry project is conducted by the ESICM H1N1 Flu Registry on Intensive Care in cooperation with the ESICM Task Force on ICU Triage for Pandemic Influenza and other disasters and the Working Group on Pneumonia. Further information can be found at the website of the project.

The project is coordinated by Jordi Rello (Tarragona, Spain). A Coordination and Communications Centre (CCC) has been installed. The CCC is composed, besides the project leader, by at least one project assistant. Further staffing as necessary will be decided by the project coordinator and the Steering Group.

The CCC will be responsible for the management and control of the whole project. This includes:

- Administration of all project tasks and implementation of actions and activities as necessary.
- Communication between project partners (e.g. centres, researchers and institutions) through sampling and distribution of necessary information.
- Pooling and administration of the data from the various project participants.

The CCC is located in Tarragona, Spain and the address of the CCC is:

H1N1 Registry Coordination Center

Servicio de Medicina Intensiva – Hospital Universitari Joan XXIII

Carrer Mallafre Guasch, 4 – 1^a planta

Tarragona – Spain

43007

Fax: +34 977 216395

Email: info@h1n1registry.com

6.2. Steering Group

The Steering Group is responsible for the scientific conduct and consistency of the project. It is moreover the communication interface between the project research group and the European Society of Intensive Care Medicine. The Steering Group consists of:

- Jordi Rello, Tarragona, Spain
- Rui Moreno, Lisboa, Portugal
- Andrew Rhodes, London, UK
- Charles Sprung, Jerusalem, Israel
- Thiago Lisboa, Tarragona, Spain
- Eliezer Silva, Sao Paulo, Brazil
- Charles Gomersall, Hong Kong

6.3. Advisory Board

The Advisory board integrates scientists with a special expertise and capabilities with respect to the conduct of the project. Members of the advisory board should comment on the scientific content of the project and help with their expertise in conducting the project successfully. It consists of:

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- Jean-Daniel Chiche, Paris, France
- George Dimopoulos, Athens, Greece
- Rosa Reina, Buenos Aires, Argentina
- Robert Fowler, Toronto, Canada
- Francisco Arancibia, Santiago, Chile
- Alejandro Rodriguez, Tarragona, Spain
- Jeffrey Lipman, Brisbane, Australia
- Antonio Anzueto, San Antonio, Texas

6.4. Country Coordinators

During the development of the project, the operational management at country level is the responsibility of the country coordinators. The country coordinator is the direct communication partner of the ICU coordinators within his/her country and is responsible for:

- Distribution of research manuals and other materials.
- Distribution of the CRF for cases notification in country level
- Communicate the new cases to CCC to provide access to electronic database for the users;
- Getting the approval from the respective national ethics or data-protection committee when applicable. We consider a waiver of informed consent should be sought as there are no treatments involved and patients remain anonymous.
- Collecting of the data from the different ICUs and forwarding them to the Coordination Centre.
- Controlling the completion of the different tasks by the participating ICUs.
- General communication with the participating ICUs in his/her country, involving specific help where necessary.
- Nomination of an ICU coordinator for each participating ICU in his/her country.

6.5. ICU Coordinators

The ICU coordinators are the respective people at each ICU, who are responsible for the local activities. They might belong to the medical or non-medical staff of the unit. Their responsibilities involve:

- Getting the approval from the respective local ethics or data-protection committee when applicable;
- Supervision of the daily data collection and problem management.
- Send Case Report Form to National Coordinator.
- Controlling the completeness of the data in electronic database.
- Data quality control.
- Training of involved medical and non-medical staff for the undertaking of data collection.
- Management of the data and transmission to the Coordination Centre / country coordinator.
- Communication with the country coordinator.

The nomination of the ICU coordinators is the responsibility of the respective country coordinators.

7. TASKS AND SCHEDULES

During this stage of the project, the main tasks and schedules are:

06/2009 - 07/2009

- Nomination of the project coordinator, the Steering Group and the Advisory Board
- Preparation of the research proposal
- Nomination of the country coordinators
- Installation of the Coordination and Communications Centre
- Development of the ICU evaluation questionnaire
- Development and adaptation of the data collection software, including data specification and programming of data collection software
- Communication network development (website content, data security locks, and communication testing)
- Software testing and software pilots

08/2009 - 03/2010

- Data collection
- Data validation with automatic checking for errors

04/2010 - 05/2010

- Data analysis

06/2010 - 07/2010

- Preparation of the final results
- Dissemination of the final report

8. DELIVERABLES

The H1N1 Registry will allow the development of an extended body of knowledge describing the main clinical characteristics of patients infected with H1N1 virus in ICU setting. This knowledge will be disseminated within the scientific community, allowing a better evaluation of these critically ill patients and contributing to improve its management.

Three main types of deliverables will be produced:

- The first type of deliverables will be scientific reports for general and specialty journals reporting on the preliminary findings.
- The second type of deliverable will be submission of abstracts for presentation to national and European intensive care conferences
- The third type of deliverables will be the final report, which will summarize the findings and highlight priorities for research for the future.

9. PUBLICATION RULES

4.1. Publication Advisory Board

A publication advisory board (PAB) will be installed to provide systematic and objective guidelines for any publication resulting either from the H1N1 Registry project or from parts of it. The PAB consists of two members and one chairman, which are all designated by the Steering Group. The project leader has the right to refuse nominations. In this case, the Steering Group has to nominate another person.

The PAB's first task will be to distribute the H1N1 Registry research project proposal. It will continue to exist until no further publications or other deliverables, regarding the H1N1 registry project are produced.

The responsibilities of this board are to review all manuscripts, which are derived from the H1N1 project, data from the H1N1 project or any part of the H1N1 project. The PAB gives and the respective authors receive, recommendations from this board, regarding:

- The adequacy in the use of the data.
- The scientific quality of the manuscript.
- The accordance of the submitted manuscript with the author's rights, as outlined below.

The recommendations of the PAB are mandatory for all authors. The PAB will always be responsible to answer any request within the shortest time possible.

4.2. Authors Rights and Duties

Authors wishing to publish manuscripts that contain data or knowledge derived from the H1N1 Registry research project or parts from it, must agree to the following rules:

- All authors rights regarding publications of deliverables, derived from the H1N1 Registry project, including data from the H1N1 project or any other knowledge or part of the H1N1 project belong to the ESICM.
- Any participant may prepare a publication regarding the H1N1 Registry project, involving the pooled data in the databank, after the PAB has been consulted and approved the publication project.
- All types of manuscripts and other deliverables have to be submitted to the PAB prior to any other publication.
- Further submission of a manuscript is only permitted with an official, written allowance of the PAB.
- Recommendations of the PAB have to be respected by the authors.

10. SCIENTISTS AGREEMENT

The success of the H1N1 Registry research project is strongly dependent upon open and transparent communication between all the participants in this project. For this reason, all participants must agree on the following issues.

5.1. Information Handling

All information and data which are collected, transferred and exchanged during the H1N1 Registry research project - or in close relation with this project - are restricted to the participants in the project and are exclusively used to serve this project. Permission of the Steering Committee is necessary, when restricted information will have to be provided to individuals, institutions or authorities outside the project.

5.2. Databank

The Steering Committee developed a H1N1 Registry project databank, which contain all the data related to the H1N1 Registry research project. This databank will contain all collected and pooled data from participating ICUs.

- The individual data, provided by a participating ICU are primarily property of the ICU who generated the data.
- The Steering Committee has the right to use all data that are pooled in the databank for scientific and other purposes.
- All participants of the H1N1 Registry research project have the right to access the data, pooled in the databank, for research purposes after the research project has been reviewed and approved by the PAB (see chapter 9, Publication Rules).
- A copy of the databases generated by the project can only be provided to third-part entities after specific approval by the participating ICUs.

11. BUDGETING AND FINANCES

Software for data collection and reporting

An agreement has been made with Onmedic (Spain) to develop and distribute an Internet-based system for data collection and distribution. This web-based resource, incorporating extensive logical and error-checking algorithms, will be available free of charges to all participating ICUs. Cost of web-based resource development will be supported by ESICM.

The electronic version of the documentation and help-files were developed by the SC and will also be distributed free of charges to all participating ICUs.

12. SPONSORS

The H1N1 Registry project is supported by the European Society of Intensive Care Medicine (ESICM).