Delay in diagnosis of influenza A (H1N1)pdm09 virus infection in critically ill patients and impact on clinical outcome

Francisco Álvarez-Lerma¹,²,³*, Judith Marín-Corral¹,², Clara Vila¹, Joan Ramón Masclans¹,²,⁴,⁵, Francisco Javier González de Molina⁶, Ignacio Martín Loeches⁷, Sandra Barbadillo⁸, Alejandro Rodríguez⁴,⁹ and on behalf of the H1N1 GETGAG/SEMICYUC Study Group

Abstract

Background: Patients infected with influenza A (H1N1)pdm09 virus requiring admission to the ICU remain an important source of mortality during the influenza season. The objective of the study was to assess the impact of a delay in diagnosis of community-acquired influenza A (H1N1)pdm09 virus infection on clinical outcome in critically ill patients admitted to the ICU.

Methods: A prospective multicenter observational cohort study was based on data from the GETGAG/SEMICYUC registry (2009–2015) collected by 148 Spanish ICUs. All patients admitted to the ICU in which diagnosis of influenza A (H1N1)pdm09 virus infection had been established within the first week of hospitalization were included. Patients were classified into two groups according to the time at which the diagnosis was made: early (within the first 2 days of hospital admission) and late (between the 3rd and 7th day of hospital admission). Factors associated with a delay in diagnosis were assessed by logistic regression analysis.

Results: In 2059 ICU patients diagnosed with influenza A (H1N1)pdm09 virus infection within the first 7 days of hospitalization, the diagnosis was established early in 1314 (63.8 %) patients and late in the remaining 745 (36.2 %). Independent variables related to a late diagnosis were: age (odds ratio (OR) = 1.02, 95 % confidence interval (CI) 1.01–1.03, P < 0.001); first seasonal period (2009–2012) (OR = 2.08, 95 % CI 1.64–2.63, P < 0.001); days of hospital stay before ICU admission (OR = 1.26, 95 % CI 1.17–1.35, P < 0.001); mechanical ventilation (OR = 1.58, 95 % CI 1.17–2.13, P = 0.002); and continuous venovenous hemofiltration (OR = 1.54, 95 % CI 1.08–2.18, P = 0.016). The intra-ICU mortality was significantly higher among patients with late diagnosis as compared with early diagnosis (26.9 % vs 17.1 %, P < 0.001). Diagnostic delay was one independent risk factor for mortality (OR = 1.36, 95 % CI 1.03–1.81, P < 0.001).

Conclusions: Late diagnosis of community-acquired influenza A (H1N1)pdm09 virus infection is associated with a delay in ICU admission, greater possibilities of respiratory and renal failure, and higher mortality rate. Delay in diagnosis of flu is an independent variable related to death.

Keywords: Influenza A (H1N1)pdm09 virus infection, Mortality, Critically ill, Early diagnosis, Late diagnosis, Outcome, ICU

* Correspondence: F.Alvarez@parcdesalutmar.cat
¹Service of Intensive Care Medicine, Hospital del Mar, Passeig Maritim 25-29, E-08003 Barcelona, Spain
²Research Group in Critical Disorders (GREPAC), Institut Hospital del Mar d’Investigacions Mèdiques (IMIM), Barcelona, Spain
Full list of author information is available at the end of the article

© 2016 The Author(s). Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background
Since the 2009 H1N1 influenza pandemic, patients with influenza A (H1N1)pdm09 admitted to the ICU remain an important source of mortality during the influenza season [1, 2]. The importance of early diagnosis and prompt start of antimicrobial treatment has been shown consistently in critically ill patients with severe bacterial infection or severe sepsis [3–6]. In patients with influ-

enz A, in most cases typically during epidemic periods, antiviral treatment is administered when diagnosis is sus-
pected (within the first 48 hours of hospital admission), although diagnosis and treatment (between the 3rd and 7th day of admission) can be delayed because of the lack of clinical suspicion by the medical team or negative results in the first samples analyzed (false nega-
tives) [7, 8].

Different studies have identified factors independently associated with mortality in patients diagnosed with influ-

enz A (H1N1)pdm09 infection [9, 10] or in selected sub-
groups, such as patients older than 65 years of age [11], obesity [12], immunodeficiency viral infection (HIV) [13], chronic liver disease [14], childhood [15] and pregnancy [16], as well as in different presenting forms of infection (severe sepsis, septic shock, pneumonia) and ICU admis-
sion [17, 18]. Also, other subsets of patients have been in-
dependently analyzed according to the presence of some factors, such as previous influenza vaccination [19], earli-
ness of treatment with oseltamivir [20], use of corticoids [21] or macrolides [22], or the need for invasive or nonin-
vasive mechanical ventilation on ICU admission or during the ICU stay [23]. However, the clinical impact of a delay in the diagnosis of influenza A (H1N1)pdm09 virus infec-
tion is unknown, particularly in those patients ultimately requiring admission to the ICU.

The objective of the study was to analyze data available in a multicenter database of patients admitted to the ICU diagnosed with influenza A (H1N1)pdm09 virus infection, to determine clinical factors related to a delay in diagnosis and the impact on the outcome of patients. It was hypothe-
sized that a delay in diagnosing influenza A (H1N1)pdm09 infection is associated with a worse clinical course and that early identification of influenza-infected patients can contribute to optimization of treatment.

Methods
Design and study population
This was a prospective, multicenter, observational cohort study. Between January 1, 2009 and December 31, 2015, data for all patients with microbiologically-confirmed diagnosis of influenza A (H1N1)pdm09 virus infection admitted to 148 ICUs throughout Spain were included in the GETGAG/SEMICYUC registry (Spanish Working Group on Severe Pandemic Influenza A (GETGAG) of the Spanish Society of Critical Care Medicine and Coronary Units (SEMICYUC)). All patients with influenza symptoms admitted to the participating ICUs were tested for influenza A or B, and investigators voluntarily registered all influenza A (H1N1)pdm09-positive pa-
tients in the national registry. The identification of pa-
tients was anonymized and individual patient informed consent was not obtained given the noninterventional nature of the study. The GETGAG/SEMICYUC registry was approved by the Institutional Review Board of Hos-
pital Joan XXIII University Hospital of Tarragona, Spain.

All patients admitted to the ICU with clinical manifes-
tations of respiratory infection in which influenza A (H1N1)pdm09 virus was identified during the first week of hospital stay were included in the study. The presence of influenza A (H1N1)pdm09 virus was confirmed by real-
time polymerase chain reaction (rt-PCR) performed ac-
cording to recommendations of the Centers for Disease Control and Prevention (CDC) [24]. Clinical manifesta-
tions included two or more of the following signs and symptoms: fever (>38 °C), cough, bronchial expectoration, and myalgias associated with clinical signs of organ or sys-
tem failure (respiratory failure, renal failure, altered consciousness). Exclusion criteria were patients younger than 15 years of age, patients diag-
nosed with influenza A (H3N2) or influenza B, and pa-
tients in whom diagnosis of influenza A (H1N1)pdm09 virus infection had been established from 7 days of hos-
pital admission.

Definitions
Patients included in the study were classified into two groups according to the time at which the diagnosis of influenza A infection was made: early (within the first 2 days of hospital admission) and late (between the 3rd and 7th day of hospital admission). Definition of community-
acquired pneumonia was based on recommendations of the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) [25].

Case report form
A case report form (CRF) was designed for data collection, including demographics (age, sex), time-related variables (time between hospital admission and diagnosis of influenza A, length of hospital stay before ICU admis-
sion, length of ICU stay, total length of hospital stay), comorbidities, previous influenza vaccination, epidemics season (2009–2012, 2013–2015), severity of illness, pre-
senting manifestations of infection (pneumonia, severe asthma, acute exacerbation episode of a chronic pul-
monary disease, heart failure), treatments administered (antivirals, inotropic drugs, corticoids, mechanical ventila-
tion, extrarenal depuration procedures), and intra-ICU mortality. The severity of infection was assessed according to the Acute Physiology and Chronic Health Evaluation
(APACHE II) score [26] and the Sequential Organ Failure Assessment (SOFA) score [27] on ICU admission. Information was provided by physicians of the participating ICUs according to the patient’s medical history, laboratory data, and radiological findings. The predicted mortality (based on APACHE II score) in the early and late diagnosis groups versus the observed mortality was calculated using the online APACHE II calculator (http://clincalc.com/IcuMortality/APACHEII.aspx).

**Statistical analysis**

Categorical variables are expressed as frequencies and percentages, and continuous variables as mean and standard deviation (SD) when data followed a normal distribution or as median and interquartile range (25th–75th percentile) when the distribution departed from normality. Differences between groups were analyzed with the chi-square ($\chi^2$) test or the Fisher’s exact test for categorical variables, and the Student’s $t$ test or the Mann-Whitney $U$ test for continuous variables. Significant variables in the bivariate analysis were included in a multivariate logistic regression analysis. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated. Cumulative survival for patients with influenza A (H1N1)pdm09 virus infection according to time of diagnosis was assessed using the Kaplan–Meier plot. Statistical significance was set at $P < 0.05$. Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) for Windows 15.0.

**Results**

A total of 2421 patients diagnosed with influenza A (H1N1)pdm09 virus infection were included in the GETGAG/SEMICYUC registry. The diagnosis was established within the first week of hospital admission in 2059 (85.0 %) patients, 1314 (63.8 %) of whom were classified into the early diagnosis group and 745 (36.2 %) into the late diagnosis group (Fig. 1). Patients in the late diagnostic group, compared with those in the early diagnosis group, were significantly older, showed higher severity of illness, higher percentages of immunosuppression, hematological diseases, and chronic renal failure, required longer hospital and ICU stay, required invasive and noninvasive mechanical ventilation more frequently, required use of vasoactive drugs, corticoids, and extrarenal depuration procedures, and treatment with oseltamivir was prescribed more lately (Table 1).

In the logistic regression analysis, independent variables related to a delay in diagnosis of influenza A (H1N1)pdm09 virus infection were as follows: age (OR = 1.02, 95 % CI 1.01–1.03, $P < 0.001$); first seasonal epidemics (2009–2012) (OR = 2.08, 95 % CI 1.64–2.63, $P < 0.001$); stay of in-patient care before ICU admission (OR = 1.26, 95 % CI 1.17–1.35, $P < 0.001$); and need for mechanical ventilation (OR = 1.58, 95 % CI 1.17–2.13, $P = 0.002$) and continuous venovenous hemofiltration (OR = 1.54, 95 % CI 1.08–2.18, $P = 0.016$) (Table 1). Patients admitted to the ICU within the first 48 hours of hospitalization showed a mean (SD) APACHE II score of 15 (7) vs 18 (8) for patients admitted after the first 48 hours ($P < 0.001$). Also, the mortality rate was significantly different between ICU admission within 48 hours of hospitalization and after 48 hours (19.4 % vs 35.2 %, $P < 0.001$).

The intra-ICU mortality was 17.1 % in the early diagnosis group (predicted 22 %) and 26.9 % in the late diagnosis group (predicted 23.5 %) ($P < 0.001$). Time to event analysis showed an association between timing of influenza A (H1N1)pdm09 diagnosis and mortality (Fig. 2), although in both groups mortality was related to the severity level (APACHE II score) on ICU admission (Fig. 3). Independent of the severity level on admission, mortality was significantly higher in the late diagnostic group for APACHE II scores of 0–10 and 21–30. Statistical significance was almost reached for APACHE II score of 11–20 ($P = 0.062$) and was not significant for scores >30 (Fig. 3). A further subanalysis regarding delay in oseltamivir therapy in relation to the date on which influenza A infection was diagnosed showed no significant differences in mortality (≤1 day vs >1 day, 17.9 % vs 22.8 %, $P = 0.153$; ≤2 days vs >2 days, 19.0 % vs 23.3 %, $P = 0.085$; ≤3 days vs >3 days, 20.6 % vs 23.2 %, $P = 0.222$). In relation to immunosuppression, the mortality rate was higher in the group of late diagnosis of influenza A (H1N1)pdm09 virus infection than in the early diagnosis group both in the presence of immunosuppression (55.2 % vs 40.6 %, $P = 0.046$) and in the absence of immunosuppression (22.7 % vs 14.9 %, $P = 0.001$).

As shown in Table 2, independent factors significantly associated with intra-ICU mortality in patients diagnosed with influenza A (H1N1)pdm09 virus infection within the first week of hospital admission included the following: late diagnosis (OR = 1.36, 95 % CI 1.03–1.81, $P < 0.001$); APACHE II score on ICU admission (OR = 1.09, 95 % CI 1.07–1.11, $P < 0.001$); hematological disease (OR = 1.98, 95 % CI 1.23–3.19, $P < 0.001$); need for mechanical ventilation (OR = 4.84, 95 % CI 2.73–8.56, $P < 0.001$); and use of continuous venovenous hemofiltration (OR = 4.81, 95 % CI 3.31–7.01, $P < 0.001$).

**Discussion**

This study shows that diagnostic delay of community-acquired influenza A (H1N1)pdm09 virus infection in critically ill patients admitted to the ICU is a risk factor for mortality. Late versus early diagnosis of influenza was associated with more days of hospitalization before ICU admission, greater need for respiratory support and extrarenal depuration techniques, as well
as longer durations of stay in the ICU and in the hospital.

The selection of 7 days as a time limit for considering the community setting as the source of influenza A (H1N1)pdm09 virus infection is based on the limit established for the incubation period of the virus [28]. The incubation period estimated for the healthy population ranges between 2 and 4 days [29, 30], although in adult patients and in immunosuppressed patients a more prolonged period has been described [31]. The present study therefore considered that the origin of infection was the community for all patients with compatible symptoms of respiratory tract infection in whom a definitive diagnosis of influenza A (H1N1)pdm09 was made within the first week of hospital admission, whereas the origin was probably nosocomial when diagnosis was established from the second week of hospital admission.

Although the study was not designed to assess causes of delay in diagnosis of influenza A (H1N1)pdm09 virus infection (specific reasons were not included in the registry), it is likely that late diagnosis may be related to the lack of clinical suspicion of viral infection or to negative results in the respiratory samples initially analyzed. The first case usually corresponds to patients with suspicion of bacterial infections treated empirically with antimicrobials with poor clinical response, and the second case to difficulties in obtaining and/or processing adequate samples. In the first publications of patients admitted to the ICU with influenza A (H1N1)pdm09 virus infection during the 2009 H1N1 influenza pandemic, upper respiratory samples were negative in up to 20% of cases, so the definitive diagnosis could have been established in samples recovered from the lower respiratory tract [7, 8]. Obtaining new samples from bronchial aspirates is thus recommended for patients with suspected severe viral pneumonia and negative oropharyngeal samples, and bronchoalveolar lavage samples should be collected only if results of bronchial aspirates are persistently negative [32].

In our country, we found a decrease in the number of patients with late diagnosis during the second influenza epidemic season, which may be due to a training effect in the management of patients with clinical suspicion of influenza A (H1N1)pdm09 virus infection especially during outbreaks and due to greater availability of techniques for rapid diagnosis.

In the present study, clinical characteristics associated with diagnostic delay of influenza A (H1N1)pdm09 were examined. Although clinically relevant differences between patients in the early and late diagnosis groups were found for a number of variables in the univariate analysis, only age, seasonal period, mechanical ventilation, continuous venovenous hemofiltration, and days until ICU admission were predictors of diagnostic delay in the logistic regression analysis. In our study there was a quite long interval between the day of blood sampling and the onset of treatment with oseltamivir even in the early diagnostic group, which may indicate that in most cases treatment was not started until the physician in charge was aware of positivity of influenza A (H1N1)pdm09 testing. Other reasons for late diagnosis, such as low degree of vigilance or false negative tests, were not recorded. Also, it has been shown that patients admitted to the ICU within the first 48 hours of hospitalization had a significantly lower severity level and mortality than those admitted to the ICU after 48 hours of hospitalization. According to these findings, a high level of clinical suspicion of influenza A (H1N1)pdm09 infection in patients at risk during flu outbreaks is needed, to establish the diagnosis as soon as possible and to reduce both delayed admission to the ICU and
### Table 1 Descriptive characteristics of patients admitted to the ICU with early or late diagnosis of influenza A (H1N1)pdm09 virus infection and independent factors related to diagnostic delay

| Variable | Early diagnosis (≤2 days) | Late diagnosis (3–7 days) | P value | Odds ratio (95% confidence interval) | P value |
|----------|----------------------------|---------------------------|---------|-------------------------------------|---------|
| Total patients | 1314 | 745 | | | |
| Age (years), mean (SD) | 48.43 (15.6) | 51.23 (15.0) | 0.001 | 1.02 (1.01–1.03) | 0.001 |
| Sex | | | | | |
| Men | 744 (56.6) | 458 (61.4) | 0.032 | | |
| Women | 570 (43.4) | 287 (38.5) | | | |
| Seasonal period | | | | | |
| 2009–2012 | 732 (59.4) | 499 (40.5) | 0.001 | 2.08 (1.64–2.63) | 0.001 |
| 2013–2015 | 582 (70.3) | 246 (29.7) | | | |
| Influenza vaccine | 60 (4.6) | 44 (5.9) | 0.169 | | |
| Comorbid conditions | | | | | |
| Asthma | 148 (11.3) | 72 (9.7) | 0.262 | | |
| Chronic obstructive pulmonary disease | 235 (17.9) | 159 (21.4) | 0.054 | | |
| Heart failure | 122 (9.3) | 84 (11.3) | 0.146 | | |
| Chronic renal failure | 81 (6.2) | 69 (9.2) | 0.013 | | |
| Hematological disease | 66 (5.0) | 64 (8.6) | 0.001 | | |
| Obesity | 459 (34.9) | 269 (36.1) | 0.574 | | |
| Diabetes mellitus | 189 (14.4) | 116 (15.6) | 0.432 | | |
| Human immunodeficiency virus infection | 32 (2.4) | 15 (2.0) | 0.540 | | |
| Neuromuscular disease | 39 (3.0) | 16 (2.2) | 0.269 | | |
| Autoimmune disease | 41 (3.1) | 28 (3.8) | 0.381 | | |
| Immunosuppression | 105 (8.0) | 102 (13.7) | 0.001 | | |
| Pregnancy | 53 (4.0) | 29 (3.9) | 0.879 | | |
| APACHE II score, mean (SD) | 15 (7) | 16 (8) | 0.001 | | |
| SOFA score, mean (SD) | 6 (3) | 6 (4) | 0.001 | | |
| Presenting clinical manifestations | | | | | |
| Primary viral pneumonia | 1129 (85.9) | 603 (81.0) | 0.004 | | |
| Coinfection (bacterial pneumonia) | 219 (16.7) | 133 (17.9) | 0.458 | | |
| Noninvasive mechanical ventilation | 482 (36.7) | 314 (42.2) | 0.022 | | |
| Mechanical ventilation | 864 (65.0) | 569 (76.4) | 0.001 | 1.58 (1.17–2.13) | 0.002 |
| Days on mechanical ventilation, median (IQR) | 8 (2–15) | 9 (4–20) | 0.001 | | |
| Vasoactive drugs | 639 (48.6) | 425 (57.0) | 0.001 | | |
| Decubitus prono | 233 (17.7) | 143 (19.5) | 0.382 | | |
| Continuous venovenous hemofiltration | 103 (7.8) | 95 (12.8) | 0.001 | 1.54 (1.08–2.18) | 0.016 |
| Corticoids | 527 (40.1) | 335 (45.0) | 0.043 | | |
| Days on corticoids, median (IQR) | 7 (4–10) | 7 (5–12) | 0.071 | | |
| Days until ICU admission, median (IQR) | 1 (1–1) | 1 (1–3) | 0.001 | 1.26 (1.17–1.35) | 0.001 |
| Length of ICU stay (days), median (IQR) | 8 (4–17) | 10 (5–20) | 0.001 | | |
| Length of hospital stay (days), median (IQR) | 14 (8–25) | 18 (10–30) | 0.001 | | |
| Days until oseltamivir therapy, median (IQR) | 4 (2–6) | 5 (3–7) | 0.001 | | |
| Mortality rate | 225 (17.1) | 200 (26.9) | 0.001 | | |

Data expressed as frequencies (percentages) unless otherwise stated.
APACHE Acute Physiology and Chronic Health Evaluation, IQR interquartile range (25th–75th percentile), SD standard deviation, SOFA Sepsis-related Organ Failure Assessment.
specific treatment with oseltamivir. Patients at risk include nonvaccinated patients (which in our study have been most of the patients in both groups) and patients in whom vaccination is recommended.

The overall intra-ICU mortality was significantly higher in the late diagnosis group. The predicted mortality based on APACHE II score on ICU admission was higher (22 %) than the observed mortality (17.1 %) in the early diagnosis group, but lower in the late diagnosis group (23.5 % vs 26.9 %). The reason why delay in diagnosis of influenza A (H1N1)pdm09 virus infection is associated with worse outcome is unclear, and a number of factors including a difference in days until oseltamivir therapy, delay in ICU admission, high severity of illness, some comorbidities, or other unidentified variables could have played a complementary role. Patients in the late diagnosis group showed higher APACHE II and SOFA scores on ICU admission, but data for severity of illness on hospital admission were not recorded, so it is unknown whether patients were already more severe on

---

**Fig. 2** Kaplan–Meier survival curves for critically ill patients admitted to the ICU with confirmed influenza A (H1N1)pdm09 in the early and late diagnostic groups

**Fig. 3** Relationship between severity of illness on ICU admission (APACHE II score) and mortality in the early and late diagnosis of influenza A (H1N1)pdm09 virus infection. APACHE Acute Physiology and Chronic Health Evaluation
| Variable                        | Survivors | Patients who died | P value | Odds ratio (95 % confidence interval) | P value |
|--------------------------------|-----------|-------------------|---------|--------------------------------------|---------|
| Total patients                 | 1528      | 395               |         |                                      |         |
| Age (years), mean (SD)         | 48.32 (15.24) | 53.08 (15.51)    | 0.001   |                                      |         |
| Sex                            |           |                   |         |                                      |         |
| Men                            | 865 (56.6) | 255 (64.6)        | 0.004   |                                      |         |
| Women                          | 662 (43.4) | 140 (35.4)        |         |                                      |         |
| Seasonal period                |           |                   |         |                                      |         |
| 2009–2012                      | 941 (80.7) | 225 (19.3)        | 0.053   |                                      |         |
| 2013–2015                      | 587 (77.5) | 170 (22.5)        |         |                                      |         |
| Influenza vaccine              | 65 (4.3)  | 26 (6.6)          | 0.137   |                                      |         |
| Comorbid conditions            |           |                   |         |                                      |         |
| Asthma                         | 113 (11.6) | 18 (6.6)          | 0.019   |                                      |         |
| Chronic obstructive pulmonary disease | 291 (19.0) | 73 (18.5)        | 0.824   |                                      |         |
| Heart failure                  | 140 (9.2)  | 53 (13.4)         | 0.011   |                                      |         |
| Chronic renal failure          | 82 (5.4)   | 53 (13.4)         | 0.001   |                                      |         |
| Hematological disease          | 65 (4.3)   | 52 (13.2)         | 0.001   | 1.98 (1.23–3.19)                     | 0.001   |
| Obesity                        | 523 (34.2) | 139 (35.2)        | 0.683   |                                      |         |
| Diabetes mellitus              | 212 (13.9) | 65 (16.5)         | 0.183   |                                      |         |
| Human immunodeficiency virus infection | 26 (1.7)  | 17 (4.3)          | 0.002   |                                      |         |
| Neuromuscular disease          | 44 (2.9)   | 11 (2.8)          | 0.929   |                                      |         |
| Autoimmune disease             | 45 (2.9)   | 20 (5.1)          | 0.036   |                                      |         |
| Immunosuppression              | 99 (6.5)   | 89 (22.5)         | 0.001   |                                      |         |
| Pregnancy                      | 64 (4.2)   | 11 (2.8)          | 0.203   |                                      |         |
| APACHE II score, mean (SD)     | 14 (6)     | 21 (8)            | 0.001   | 1.09 (1.07–1.11)                     | 0.001   |
| SOFA score, mean (SD)          | 5 (3)      | 8 (4)             | 0.001   |                                      |         |
| Presenting clinical manifestations |         |                   |         |                                      |         |
| Primary viral pneumonia        | 1273 (83.3) | 342 (86.6)     | 0.105   |                                      |         |
| Coinfection (bacterial pneumonia) | 229 (15.0) | 96 (24.3)       | 0.001   |                                      |         |
| Noninvasive mechanical ventilation | 527 (34.75) | 141 (35.7)    | 0.330   |                                      |         |
| Mechanical ventilation         | 812 (53.1) | 366 (92.7)        | 0.001   | 4.84 (2.73–8.56)                     | 0.001   |
| Vasoactive drugs               | 664 (43.5) | 307 (77.7)        | 0.001   |                                      |         |
| Decubitus prono                | 206 (13.05) | 133 (33.7)      | 0.001   |                                      |         |
| Continuous venovenous hemofiltration | 67 (4.4)  | 116 (29.4)       | 0.001   | 4.81 (3.31–7.01)                     | 0.001   |
| Corticoids                     | 500 (32.7) | 196 (49.6)        | 0.001   |                                      |         |
| Days until ICU admission, median (IQR) | 1 (1–2)   | 1 (1–3)           | 0.001   | 1.05 (0.99–1.11)                     | 0.117   |
| Length of ICU stay (days), median (IQR) | 8 (4–18)  | 9 (4–18)         | 0.660   |                                      |         |
| Length of hospital stay (days), median (IQR) | 16 (10–30) | 11 (5–21)    | 0.001   |                                      |         |
| Days until oseltamivir therapy, median (IQR) | 4 (2–6)   | 5 (3–6)          | 0.054   |                                      |         |
| Time of diagnosis              |           |                   |         |                                      |         |
| Early (≤2 days)                | 1035 (67.7) | 214 (54.2)      | 0.001   | 1.36 (1.03–1.81)                     | 0.001   |
| Late (3–7 days)                | 493 (32.3) | 181 (45.8)       |         |                                      |         |

Data expressed as frequencies (percentages) unless otherwise stated

APACHE Acute Physiology and Chronic Health Evaluation, IQR interquartile range (25th–75th percentile), SD standard deviation, SOFA Sepsis-related Organ Failure Assessment
hospital admission or worsened during hospitalization due to lack of an early diagnosis, appropriate treatment, or prompt ICU admission. Up to the present time, a number of factors related with mortality in patients diagnosed with influenza A (H1N1)pdm09 virus infection have been reported, including age, severity of illness on admission, underlying immunosuppression, delay in starting specific antiviral treatment (oseltamivir), duration of symptoms before the initiation of treatment, presence of hematological or cardiac disease, need for mechanical ventilation or extrarenal depuration techniques, and dyspnea or signs of alteration of the central nervous system on admission, among others. The present study provides the first observation that a delay in the diagnosis of influenza A (H1N1)pdm09 may be an independent factor associated with a higher mortality rate. Our data are complementary to other observations in which mortality is related with a delay in starting antiviral treatment and a greater duration of clinical signs of infection prior to diagnosis of infection by influenza A (H1N1)pdm09 virus [20]. For this reason, in critically ill patients admitted to the ICU and because of the increase in mortality associated with a delay in diagnosis, it is recommended to initiate antiviral treatment on diagnostic suspicion [32, 33].

Some limitations of the study should be taken into account. Firstly, the classification used for defining early and late diagnosis is based on epidemiological and microbiological considerations (viral shedding time) upon which there is no consensus in the literature. The selection of 48 hours was arbitrary. Considering that the criterion to define the time of diagnosis of influenza A was the day of blood sampling that allowed the identification of infection, and because this technique is not available in the emergency laboratories of some Spanish hospitals, 48 hours was assumed as the cutoff point given that in many centers a sample for PCR assay was electively collected on the next day of admission to the emergency department. However, a further analysis with early diagnosis at ≤24 hours and late diagnosis at 2–7 days showed similar results (data not shown). Differences in clinical characteristics and outcome between patients in the early and late diagnostic groups emphasize the need for including this classification to homogenize risk groups in future studies. On the other hand, retrospective analysis of an epidemiological prospective database prevents the inclusion of new variables that might have been of help to define the proposed classification. The multicenter design of the study in which a therapeutic protocol has not been established previously may be associated with treatment bias, given that treatments considered most adequate were those used by each participating group. Moreover, certain variability in the interpretation of clinical signs might be present, although consensualized definitions were used for most variables.

**Conclusions**

This study shows important differences in patients diagnosed with influenza A (H1N1)pdm09 virus infection depending on the speed with which the infection is diagnosed. Late diagnosis of community-acquired influenza A (H1N1)pdm09 infection is associated with a higher severity of illness, delay in ICU admission, need for therapeutic resources, greater duration of ICU and hospital stay, and, more importantly, higher intra-ICU mortality. The present findings highlight the need during the epidemiological seasons for an early diagnosis of influenza A (H1N1)pdm09 and prompt antiviral treatment in all hospitalized patients with signs of respiratory infection, independently of other clinical diagnoses.

**Abbreviations**

APACHE II: Acute Physiology and Chronic Health Evaluation; CDC: Centers for Disease Control and Prevention; CI: Confidence interval; GETGAG: Spanish Working Group on Severe Pandemic Influenza A; HIV: Human immunodeficiency virus; ICU: Intensive care unit; OR: Odds ratio; r-PCR: Real-time polymerase chain reaction; SEMICYUC: Spanish Society of Critical Care Medicine and Coronary Units; SOFA: Sepsis-related Organ Failure Assessment

**Acknowledgements**

This article was presented at the LI Annual Congress of the SEMICYUC, Valencia, Spain, June 19–22, 2016 and at the 29th European Society of Intensive Care Medicine (ESICM), Milan, Italy, October 14, 2016 (abstract accepted).

The authors thank all healthcare personnel involved in the care of patients with influenza A (H1N1)pdm09 virus infection during their stay in the ICU and who endeavored to follow the recommendations to reduce transmission of influenza A infection. They are indebted to physicians responsible for entering data into the GETGAG/SEMICYUC registry for their valuable collaboration, and Marta Pulido, MD, for editing the manuscript and editorial assistance. The fees for medical editing were paid by Fundación IMIM, Barcelona, Spain.

**H1N1 GETGAG/SEMICYUC Study Group** (alphabetical order by Autonomous Community):

**Andalucía**

Pedro Cobo (Hospital Punta de Europa, Algeciras); Javier Martín (Hospital Santa Ana Motril, Granada); Cecilia Carbayo (Hospital Torrecárdena, Almería); Emilio Robles-Musso, Antonio Cárdenas, and Javier Fierro (Hospital del Poniente, Almería); Dolores Ocaña Fernández (Hospital Huelva-Cural, Almería); Rafael Sierra (Hospital Puerta del Mar, Cádiz); Mª Jesús Huertos and Mª Luz Cardona Pérez (Hospital Puerto Real, Cádiz); Juan Carlos Pozo Laderas, R. Guerrero, Juan Carlos Robles, Melissa Echevarría León, and Alberto Bermejo Gómez (Hospital Reina Sofia, Córdoba); Enrique Márquez (Hospital Infantaria Elena, Huelva); Manuel Rodríguez-Canovas (Hospital Juan Ramón Jiménez, Huelva); Ángel Estrella (Hospital del SAS de Jerez, Jerez del la Frontera); José Pomezas, José Luis Ballesteros, and Olga Moreno Romero (Hospital Universitario San Cecilio, Granada); Yolanda Fernández, Francisco Lobato, José F. Prieto, and José Albovedo-Sánchez (Hospital Costa del Sol, Marbella, Málaga); Pilar Martín, María Victoria de la Torre, María Nieto, and Estefanía Cámaria Sola (Hospital Virgen de la Victoria, Málaga); Miguel Ángel Díaz Castellanos (Hospital Santa Ana de Motril, Granada); Guillermo Sevilla Soler and Carlos Ortiz Leyba (Clínica Sagrado Corazón, Málaga); José Garmache-Montero, Rafael Hinojosa, and Esteban Fernández (Hospital Universitario Virgen del Rocío, Sevilla); Ana Loza, Cristobal León, and Samuel González López (Hospital Universitario Nuestra Señora de Valme, Sevilla); Ángel Arenaza (Hospital Virgen de la Macarena, Sevilla); Dolores Ocaña (Hospital de la Inmaculada, Sevilla); Inés Navañete (Hospital Virgen de las Nieves, Granada); Medhi Zaheri Beryanaki (Hospital de Antequera, Málaga); Ignacio Sánchez and Manuel Pérez Alé (Hospital Nisa Sevilla Aljarafe, Sevilla);
Ana Mª Poulet Brea (Hospital Quirón Málaga, Málaga); y Juan Francisco Machado Casas (Complejo Hospitalario de Jaén, Jaén).

Aragón
Carlos Serón, Manuel Luis Avellanaz, Arantxa Landet, S. Garrido Ramírez de Anellano, y M.J. Marquina Lacueva (Hospital San Jorge, Huesca); Pilar Luque, Elena Plumere Serrano, Juan Francisco Martín Lázaro, Carlos Sánchez Polo, Isabel Gutiérrez Cia, Belén Jiménez Bartolomé, y Carlos López Núñez (Hospital Clínico Universitario Lozano Blesa, Zaragoza); Ignacio González, José Ignacio Tomás Marsilla, Clara Jaques Andrés, Pablo Gutiérrez Ibáñez, y Pilar Araujo Aguilar (Hospital Universitario Miquel Servet, Zaragoza); José Mª Montón (Hospital Obispo Polanco, Teruel); y Paloma Dorado Regil (Hospital Royo Villanueva, Zaragoza).

Asturias
Unidad Igleias, Carmen Pascal González, Brigida Quintos Fernández, Lorena Martín Iglesias, Lucía Viña Soria, Raquel Yano Escudero, y Mª del Rosario Martínez Revuelta (Hospital Universitario Central de Asturias, Oviedo); José Mª Quiroga Ruíz (Hospital de Cabuérniga, Gijón); Agueda García-Rodríguez (Hospital Valle del Nalón, Langreo); y Marta Martín Cuadrado y Ana Luz Balán Martín (Hospital San Agustín, Avilés).

Baleares
Lorenzo Socías, Pedro Ibáñez, Marçol Borges-Sa, A. Socías y A. Del Castillo (Hospital Son Llàtzer, Palma de Mallorca); Ricard Jordà Marcos y Cristina Muñoz (Clínica Rotger, Palma de Mallorca); José M. Bonell Goytisolo y José Antonio Morales Carbonero (Hospital Quirón Salud Palmaplanas, Palma de Mallorca); Ignacio Ayestaran (Hospital Don Dureta, Palma de Mallorca); M. Ángeles González López y Cecilia Villanueva Pàemes (Hospital Mateu Orfila, Palma de Mallorca); y Rosanna Pérez Senoff y Marta Generelo Lépere de Medrano (Hospital Comarcal de Inca, Palma de Mallorca).

Canarias
Sergio Ruiz-Santana, Juan José Díaz, y Catalina Sánchez Ramírez (Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria); Montse Sisón (Hospital Doctor José Molina, Lanzarote); David Hernández, Ana Trujillo, Luis Regalado, y Sonia Rodríguez Fernández (Hospital General de la Palma, La Palma); Leonardo Lorente, Judith Cabrera Rivero, y Mª Luisa Mora Quintero (Hospital Universitario de Canarias, Tenerife); Mar Martín (Hospital de la Candelaria, Tenerife); Sergio González, J.J. Cáceres, y Manuel Sánchez Palacio (Hospital Insular de Gran Canaria); y D. García Rodríguez y María Ripoll Lleris (Hospital General de Fuerteventura, Fuerteventura).

Cantabria
Boja Suberviola y P. Ugarte (Hospital Universitario Marqués de Valdecilla, Santander).

Castilla La Mancha
Fernando García-López y Rafael Sánchez Iniesta (Hospital General, Albacete); Ángel Álvaro Alonso, Antonio Padilla, y Bás Martinzal Palacios (Hospital General La Mancha Centro, Alcázar de San Juan); Mª Luisa Gómez Alarcón, Mª Carmen Martín Rodríguez, Hasiana Adell-Hadi Álvarez, Alfonso Ambros Checa, y Higinio Martín Hernández (Hospital General la Palma, La Palma); Leonardo Lorente, Judith Cabrera Rivero, y Mª Luisa Mora Quintero (Hospital Universitario de Canarias, Tenerife); Mar Martín (Hospital de la Candelaria, Tenerife); Sergio González, J.J. Cáceres, y Manuel Sánchez Palacio (Hospital Insular de Gran Canaria); y D. García Rodríguez y María Ripoll Lleris (Hospital General de Fuerteventura, Fuerteventura).

Extremadura
Julián-Navas José, Manuel Robles Marcos, Vanesa Faro Mallqui, Mª Ángeles Santiago Trivio, y Pablo Martínez García (Hospital Infanta Cristina, Badajoz); Alberto Fernández-Zapata, Teresa Recio, Abilio Arraceta, Mª José García-Ramos, Elena Gallego, y Esther Saiz Rodrigo (Hospital San Pedro de Alcántara, Cáceres); Fernando Bueno (Hospital Virgen del Puerto, Plasencia, Cáceres); Mercedes Díaz, Noemi Gil Pérez, y David López Hormigo (Hospital de Mérida, Mérida); Juan Diego Jiménez Delgado (Hospital Don Benito, Villanueva de la Serena, Badajoz); Pérez Frutos y M. J. Rivera Pinna (Hospital Perpetuo Socorro, Badajoz).

Galicia
Mª Lourdes Cordero, José A. Pastor, Luis Álvarez-Rocha, Alexandra Cenércos Barros, y Alejandra Virgós Pedreira (Complejo Hospitalario Universitario A Coruña, A Coruña); Dolores Vilá (Hospital Do Meixoeiro, Vigo); Carmen Fernández González (Complejo Hospitalario Universitario de Ferrol, Ferrol, A Coruña); Eleuterio Merayo, Víctor José López-Cuad, Juan Cortés Cañones, Eva Villalob, José Villar Chao, Francisco Savia Cid López, Pablo Vidal Cortés, y Marcos A. Pérez Veloso (Complejo Hospitalario de Ourense, Ourense); Eva María Saborido, Enrique Almendare Pardavila, y Ana Ortega Montes (Hospital Montepeco, Pontevedra); Raul José González (Hospital Miguel Domínguez, Pontevedra); Santiago Freita, Enrique Almendare, y Ana Ortega (Complejo Hospitalario de Pontevedra, Pontevedra); Ana María López, Julio Canabal, y Enrique Ferrés (Clínica Universitaria Santiago de Compostela, Santiago de Compostela, A Coruña); Javier Blanco Pérez y M. Ortiz Piquer (Hospital Lucas Augusti-HULA, Lugo); Santiago Freitas Ramos, Lucas Lage Cendón, Vanesa Gómez Casal, Sabela Vara Adrio, Eva Menor Fernández, y Susana González Prado (H. Xeral-C.H.U. de Vigo, Vigo); y Antonio Varela Franco (Hospital Vithas Nuestra Señora de Fátima, Vigo).

Lugo
José Luis Monzón y Félix Goñi (Hospital San Pedro, Logroño).

Madrid
Frutos Del Nogal Sáez, M. Blasco Navalpont, Ricardo Díaz Abad, y José Luis Flor delsiers Lasierna (Hospital Severo Ochoa, Madrid); Mª Carmen García-Torrejón (Hospital Infantia Elena, Madrid); César Pérez-Calvo y Diego López (Fundación Jiménez Díaz, Madrid); Luis Arnaiz, S. Sánchez-Alonso, y Carlos
Velayos (Hospital Fuenlabrada, Fuenlabrada, Madrid); Francisco del Río, Miguel Ángel González, Mercedes Nieto, and Carmen Sánchez Cesteros (Hospital Clínico San Carlos, Madrid); María Cruz Martín and José Mª Molina (Hospital Nuestra Señora de América, Madrid); Juan Montejo and Mercedes Catalán (Hospital Universitario 12 de Octubre, Madrid); Patricia Albert and Ana de Pablo (Hospital del Sureste, Arganda del Rey, Madrid); José Eugenio Guerrero, María Zurita, Jaime Benítez Peyrat, and Miriam Díaz Cámara (Hospital Universitario Gregorio Marañón, Madrid); Enrique Cerdá, Manuel Álvarez, Carlos Pey, Eva Manteiga Riestra, and Concepción Martínez-Fidalgo (Hospital Infantia Cristina, Parla, Madrid); Montse Rodríguez and Eduardo Palencia (Hospital Infanta Leonor, Madrid); Rafael Caballero (Hospital de San Rafael, Madrid); Concepción Vaquero, Francisco Mariscal, S. García, and Ricó Cepeda (Hospital Infantia Sofia, Madrid); Nieves Carrasco (Hospital Universitario La Princesa, Madrid); Isidro Prieto, A. Lietor, R. Ramos, Rosario Cuadra Casas, Cruz Soriano Cuesta, and Susana Sánchez Alonso (Hospital Ramón y Cajal, Madrid); Beatriz Galván, Juan C. Figuerejo, M. Cruz Soriano, Bellen Civantos Martín, and Alejandro Robles Caballero (Hospital La Paz, Madrid); P. Galdós, Bárbara Balandín Moreno, and Sara Aalcantara Carnomo (Hospital Puerta de Hierro, Madrid); Fernández del Cabo (Hospital Monte Príncipe, Madrid); Cecilia Hermosa and Federico Gordo (Hospital de Henares, Madrid); Alejandro Algora (Hospital Universitario Fundación Alcorcón, Madrid); A. Cambrón, Esther López Ramos, and Yaiza Ortiz de Zárate (Hospital Universitario Príncipe de Asturias, Madrid); Sonia Gómez-Rosado, Margarita Mas Lodo, Nieves Franco Garrido, Silvia Álvarez Hernández, and Teresa Hont rubia (Hospital de Móstoles, Madrid); Luis Miguel Prado López (Hospital Sanitas La Zarzuela, Madrid); Esther A. Lorente, J.A. Nin, and Carlos Jaramillo Sotomayor (Hospital de Getafe, Madrid); Luis Arazni (Sanitas de Moraleja, Madrid); Esperanza Molero Silvero and Eduardo Morales Fernández de la Reguera (Hospital Central de la Defensa “Gómez Ulla”, Madrid); Rosa Mª de la Casa Monje and Pita Martín Herranz (Clinica Moncloa, Madrid); and Mª Victoria Tarsirmon Martínez, and M. Cruz Martín Delgado (Hospital de Torrejón, Torrejón de Ardoz, Madrid).

Murcia

Soñita Martínez (Hospital Santa María del Rosell, Murcia); F. Felices Abad, Isabel Cremaides Navalón, and Martín Vigil Velis (Hospital Universitario Reina Sofía, Murcia); Mariano Martínez, Domingo Martínez Baño, and Enrique Sánchez (Hospital Universitario Virgen de la Arrixaca, Murcia); Sergio Manuel Buti, Bernardo Gil Rueda, and Francisco García (Hospital Morales Meseguer, Murcia); Noemí Llamas Fernández (Hospital Universitario General Rafael Méndez, Lorca); Luis Herrera Para and Alejandro Ortín Freire (Hospital Universitario Santa Lucía, Cartagena); and Mª Rosa Navarro Ruiz and C.R. Martínez-Velázquez (Hospital Universitario Reina Sofía, Murcia).

Navarra

Enrique Maraví-Poma, I. Jiménez Urra, Laura Macaya Redin, and A. Tellería Nin (Hospital Virgen del Camino, Pamplona); José Insautxi (Hospital de Navarra, Pamplona); and Noelia Artesero García, Laura Macaya, and Joaquín Lobo Palanco (Complejo Hospitalario de Navarra, Pamplona).

País Vasco

Nagore González, Pilar Marzo, Loreto Vidal, Estibaliz Salas, and Ruth del Carmen (Hospital Virgen del Camino, Pamplona); Josu Sanjuán (Hospital de Navarra, Pamplona); and Noelia Artesero García, Laura Macaya, and Joaquín Lobo Palanco (Complejo Hospitalario de Navarra, Pamplona).

Valencia

José Blanquer, Nieves Carbonell, and José Ferreres Franco (Hospital Clinic Universitat, Valencia); Roberto Reig Valero, A. Belenguer, and Susana Altaja (Hospital General de Castellón, Castellón); Bernabé Álvarez-Sánchez, José Cánovas Robles, Jaime Sánchez Francisco, and Mar Ruiz Sánchez (Hospital General de Alicante, Alicante); Santiago Alberto Picó, A. Arolas and Llanes, Eugenio Herrero Gutiérrez, and Alberto Fernández Zapata (Hospital Torrevieja, Alicante); Angel Sánchez-Nifráles and José Luis Antón Pascual (Hospital San Juan, Alicante); Juan Bonastre, M. Palomar, Javier Cebrián, José Cufiat, and Mónica Gordón Sahuquillo (Hospital Universitari i Politécnic La Fe, Valencia); Belén Romero, Santiago Borrós Pallé, and Javier de León Belmar (Hospital de Manises, Valencia); Rafael Zaragoza, Constantino Tormo, and Susana Sancho Chinesta (Hospital Universitari Doctor Peset, Valencia); Virgilio Paricio (Hospital de Requena, Valencia); Asunción Marqués, S. Sánchez-Morillo, and S. Tormo (Hospital de la Ribera, Valencia); J. Latour (Hospital General Universitario de Elche, Valencia); M. Ángel García and Manuel Palomo (Hospital de Sagunto, Castellón); Francisco Tarín Royo and Pedro Manzano Hinojoa (Hospital de Denia, Alicante); Mª Salomé Sánchez Pino (Hospital Vega Baja, Alicante); and Concha Maragúes Ribes and Rubén González Luis (Hospital de la Plana, Castellón).

Antoli Ribas from Hospital Nuestra Señora de Meritxell (Andorra) was also a member of the group.

Funding

The registry for patients with influenza A has been developed by the GETGAG and is owned by the SEMICYUC (GETGAG/SEMICYUC).

Authors’ contributions

FA-L participated in the study conception and design, data collection, and interpretation of analysis and drafted the manuscript. JM-C participated in the study conception and design, statistical analysis and interpretation, and critical review of the manuscript for intellectual content. CV participated in data collection and revised the manuscript. JM participated in data collection and helped to revise the manuscript. FJdM participated in data collection and helped to revise the manuscript. IML participated in the design of the database, helped in data collection, and helped to revise the manuscript. SB participated in data collection and helped to revise the manuscript. AR participated in the study design and coordination, helped to design the database, and carried out the collection of data. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of University Hospital Joan XXIII of Tarragona, Spain. Consent statement is not applicable given the noninterventional nature of the study because data were collected retrospectively from the GETGAG/SEMICYUC registry.

Accession number to microarray data

Not applicable.

Author details

1 Service of Intensive Care Medicine, Hospital del Mar, Passeig Maritim 25-29, E-08003 Barcelona, Spain. 2 Research Group in Critical Disorders (GREPAC), Institut Hospital del Mar de Investigacions Mèdiques (IMIM), Barcelona, Spain. 3 Universitat Autònoma de Barcelona, Barcelona, Spain. 4 CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain. 5 Universitat Pompeu Fabra, Barcelona, Spain. 6 Service of Intensive Care Medicine, Hospital Universitari Mútua de Terrassa, Terrassa, Barcelona, Spain. 7 Service of Intensive Care Medicine, St James Hospital, Dublin, Ireland. 8 Service of Intensive Care Medicine, Hospital General de Catalunya, Sant Cugat del Vallés, Barcelona, Spain. 9 Service of Intensive Care Medicine, Hospital Universitari Joan XXIII, IISPV-URV, Tarragona, Spain.

Received: 21 July 2016 Accepted: 26 September 2016

Published online: 23 October 2016

References

1. Pérez-Carrasco M, Lagunes L, Antón A, Gattarello S, Laborda C, Pumarola C, et al. Influenza infection in the intensive care unit: four years after the 2009 pandemic. Enferm Infec Microbiol Clin. 2016;34:177–83.
2. Steng A, Piffert C, Weissbrich B, Liese JG, Bavarian PICU Study Group on Influenza and Other Viral ARI. Continued high incidence of children with severe influenza A(H1N1)pdm09 admitted to paediatric intensive care units in Germany during the first three post-pandemic influenza seasons, 2010/11-2012/13. BMC Infect Dis. 2015;15:573. doi:10.1186/s12879-015-1293-1.
3. Puskarič MA, Tr淄博iček S, Shapiro M, Arnold RC, Horton JM, Studnek JR, Emergency Medicine Shock Research Network (EMSHOCKNET), et al. Association between timing of antibiotic administration and mortality from Influenza infection in the intensive care unit after pandemic influenza A(H1N1)2009: the WISCONSIN study (WISCONSIN). Clin Infect Dis. 2015;60(12):1628–36.
septic shock in patients treated with a quantitative resuscitation protocol. Crit Care Med. 2011;39:2066–71.
4. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41:681–633.
5. Ferrier R, Martin-Löeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014;42:1749–55.
6. Steffing SA, Miller WR, Pryor J, Puskarchik MA, Jones AE. The impact of timing of antibiotics on outcomes in severe sepsis and septic shock: a systematic review and meta-analysis. Crit Care Med. 2015;43:1907–15.
7. Rello J, Rodriguez A, Ibáñez P, Socías L, Cebrián J, Marques A, Guerrero J, Ruiz-Santana S, et al. Intensive care adult patients with severe respiratory failure caused by influenza A (H1N1) in Spain. Crit Care. 2009;13(S):R148.
8. Rodríguez A, Sirvent JM, Socías L, Martínez-Cuellar S, Rello J. Real-time reverse-transcription PCR in the diagnosis of influenza A(H1N1)v in intensive care unit adult patients. Crit Care Med. 2009;37:1428.
9. Zhang P, Cao B, Li XL, Liang LR, Yang SG, Gu L, et al. Risk factors for adult death due to 2009 pandemic influenza A (H1N1) virus infection: A 2151 severe and critical cases analysis. Clin Med (Engl). 2013;12:2222–8.
10. Lynfield R, Davey R, Dwyer DE, Lofossi MA, Bentovitch D, Cozzi-Lepri A, INSIGHT, INSIGHT. Influenza Study Group, et al. Outcomes of influenza A(H1N1)pdm09 virus infection: results from two international cohorts. Pediatr Infect Dis J. 2014;33:e1078S.
11. Gamacho-Montoro J, Guzmán-Pizarra M, Márquez JA, Zaragoza R, Granada R, Ruiz-Santana S, et al. Epidemiology, clinical features, and prognosis of elderly adults with severe forms of influenza A (H1N1). J Am Geriatr Soc. 2013;61:1350–6.
12. Feuza L, Julio C, Henegar A, Btu J, Hu FB, Grobbe DE, et al. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. Obes Rev. 2011;12:653–9.
13. López-Aldave J, Iribarren JA, Valencia E, Barquilla E, Knobel H, Santos J, et al. Outcomes in HIV-infected patients admitted due to pandemic influenza. Enferm Infecc Microbiol Clin. 2012;30:668–12.
14. Bal CK, Bhatia V, Kumar S, Saini D, Khillan V, Gupta E, et al. Influenza A/H1N1/09 infection in patients with cirrhosis has a poor outcome: a case series. Indian J Gastroenterol. 2014;33:178–82.
15. Hernández-Bou S, Novell CI, Aliño JG, García-García JJ. Hospitalized children with influenza A (H1N1) (2009) infection: a Spanish multicenter study. Pediatr Emerg Care. 2013;29:49–52.
16. Maravi-Poma E, Martín-Löeches I, Regidor E, Laplaza C, Cambra K, Aldunate S. Severe 2009 A/H1N1v influenza in pregnant women in Spain. Crit Care Med. 2011;39:945–51.
17. Martín-Löeches I, Díaz E, Vidaur L, Torres A, Laborda C, Granada R, et al. Pandemic and post-pandemic influenza A (H1N1) infection in critically ill patients. Crit Care. 2011;15:288.
18. Rodríguez A, Martín-Löeches I, Bonastre J, Olachea P, Álvarez-Lerma F, Zaragoza R, et al. First influenza season after the 2009 pandemic influenza: report of the first 300 ICU admissions in Spain. Med Intensiva. 2011;35:208–16.
19. Arriola CS, Anderson EJ, Baumbach J, Bennett N, Bohm S, Hill M, et al. Does influenza vaccination modify influenza severity? Data on older adults hospitalized with influenza during the 2012–2013 season in the United States. J Infect Dis. 2015;212:1200–8.
20. Rodríguez A, Díaz E, Martín-Löeches I, Sandiumenge A, Canadell L, Díaz JJ, et al. Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza A. J Antimicrob Chemother. 2011;66:1140–9.
21. Díaz E, Martín-Löeches I, Canadell L, Vidaur L, Suárez D, Socías L, et al. Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. J Infect. 2012;64:311–8.
22. Martín-Löeches I, Bermejo-Martin JF, Valls J, Granada R, Vidaur L, Vergara-Serrano JC. Macrolide-based regimens in absence of bacterial co-infection in critically ill H1N1 patients with primary viral pneumonia. Intensive Care Med. 2013;39:956–9.
23. Masclans JR, Pérez M, Armíllez J, Lorente L, Marqués A, Socías L, Vidaur L, Rello J. Early non-invasive ventilation treatment for severe influenza pneumonia. Clin Microbiol Infect. 2013;19:249–56.
24. Centers for Disease Control and Prevention. (CDC). Interim Recommendations for Clinical Use of Influenza Diagnostic Tests During the 2009-2010 Influenza Season. http://www.cdc.gov/h1n1flu/guidance/diagnostic_tests.htm Accessed 26 Mar 2016.