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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S<sup>®</sup>



## Community-Acquired Respiratory Coinfection in Critically Ill Patients With Pandemic 2009 Influenza A(H1N1) Virus

Ignacio Martín-Loeches, MD, PhD; Ana Sanchez-Corral, MD; Emili Diaz, MD, PhD; Rosa María Granada, MD; Rafael Zaragoza, MD; Christian Villavicencio, MD; Antonio Albaya, MD; Enrique Cerdá, MD; Rosa María Catalán, MD; Pilar Luque, MD; Amparo Paredes, MD; Inés Navarrete, MD; Jordi Rello, MD, PhD; Alejandro Rodríguez, MD, PhD; and H1N1 SEMICYUC Working Group

**Background:** Little is known about the impact of community-acquired respiratory coinfection in patients with pandemic 2009 influenza A(H1N1) virus infection.

**Methods:** This was a prospective, observational, multicenter study conducted in 148 Spanish ICUs.

**Results:** Severe respiratory syndrome was present in 645 ICU patients. Coinfection occurred in 113 (17.5%) of patients. *Streptococcus pneumoniae* (in 62 patients [54.8%]) was identified as the most prevalent bacteria. Patients with coinfection at ICU admission were older ( $47.5 \pm 15.7$  vs  $43.8 \pm 14.2$  years,  $P < .05$ ) and presented a higher APACHE (Acute Physiology and Chronic Health Evaluation) II score ( $16.1 \pm 7.3$  vs  $13.3 \pm 7.1$ ,  $P < .05$ ) and Sequential Organ Failure Assessment (SOFA) score ( $7.0 \pm 3.8$  vs  $5.2 \pm 3.5$ ,  $P < .05$ ). No differences in comorbidities were observed. Patients who had coinfection required vasopressors (63.7% vs 39.3%,  $P < .05$ ) and invasive mechanical ventilation (69% vs 58.5%,  $P < .05$ ) more frequently. ICU length of stay was 3 days longer in patients who had coinfection than in patients who did not (11 [interquartile range, 5-23] vs 8 [interquartile range 4-17],  $P = .01$ ). Coinfection was associated with increased ICU mortality (26.2% vs 15.5%; OR, 1.94; 95% CI, 1.21-3.09), but Cox regression analysis adjusted by potential confounders did not confirm a significant association between coinfection and ICU mortality.

**Conclusions:** During the 2009 pandemics, the role played by bacterial coinfection in bringing patients to the ICU was not clear, *S pneumoniae* being the most common pathogen. This work provides clear evidence that bacterial coinfection is a contributor to increased consumption of health resources by critical patients infected with the virus and is the virus that causes critical illness in the vast majority of cases.

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**Abbreviations:** A(H1N1) = pandemic 2009 influenza A(H1N1); APACHE = Acute Physiology and Chronic Health Evaluation; CARC = community-acquired respiratory coinfection; HR = hazard ratio; IQR = interquartile range; MRSA = methicillin-resistant *Staphylococcus aureus*; PCR = polymerase chain reaction; SOFA = Sequential Organ Failure Assessment

Pandemic 2009 influenza A(H1N1) (A[H1N1]) virus infection was first described in Mexico in April 2009, and since then, several reports have been published regarding the presentation of this disease with severe acute respiratory symptoms in hospitalized patients.<sup>1</sup> Rapidly progressive viral pneumonia represents the primary cause of admission to the ICU, with mortality rates between 17.3% and 46% among different sites.<sup>1-5</sup>

Many studies have demonstrated temporal relationships between influenza activity and bacterial pneumonia. During the 1918-1919 pandemic, the bacteria

most often recovered from the sputum, lungs, and blood of pneumonia patients, alive or dead, were common colonizers of the upper respiratory tracts of healthy persons (ie, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or *Staphylococcus aureus*).<sup>6-8</sup> Moreover, substantial laboratory evidence of synergism between A(H1N1) and bacterial agents has been suggested.<sup>9</sup>

Coinfections and superinfections are common complications in persons with seasonal influenza; coinfections have been found in  $\approx 25\%$  of all influenza-related

deaths.<sup>10,11</sup> However, information regarding the impact of coinfection in patients affected with A(H1N1) virus infection is scarce. The present study evaluates whether the presence of community-acquired respiratory coinfection (CARC) in a cohort of patients hospitalized with a severe presentation of A(H1N1) virus infection in the ICU was associated with worse outcomes.

## MATERIALS AND METHODS

Study data were obtained from a voluntary registry created by the Spanish Society of Intensive Care Medicine (SEMICYUC) after the first reported ICU case. Inclusion criteria were fever ( $>38^{\circ}\text{C}$ ); respiratory symptoms consistent with cough, sore throat, myalgia, or influenza-like illness; acute respiratory failure requiring ICU admission; and microbiologic confirmation of A(H1N1). Data were reported by the attending physician reviewing the medical charts and radiologic and laboratory records. This study analyzes data from the first ICU case until December 31, 2009. Children under 15 years old were not enrolled in the study. The study was approved by the ethical board of Joan XXIII University Hospital, Tarragona, Spain. Patients remained anonymous, and the requirement for informed consent was waived because of the observational nature of the study. All tests and procedures were ordered by the attending physicians.

### Definitions

The following variables were recorded: demographic data, comorbidities, time of illness onset and hospital admission, time to first dose of antiviral delivery, microbiologic findings, and chest radiograph findings at ICU admission. Intubation and mechanical ventilation requirements, adverse events during ICU stay (eg, the need for vasopressor drugs or renal replacement therapies), and

laboratory findings at ICU admission were also recorded. To determine the severity of illness, the APACHE (Acute Physiology and Chronic Health Evaluation) II score<sup>12</sup> was determined in all patients within 24 h of ICU admission. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system.<sup>13</sup> Obese patients were defined as those with a BMI  $>30\text{ kg/m}^2$ .

Primary viral pneumonia was defined in patients presenting illness with acute respiratory distress and unequivocal alveolar opacities involving two or more lobes with negative respiratory and blood bacterial cultures during the acute phase of the influenza virus.<sup>2</sup> Nasopharyngeal-swab specimens were collected for respiratory viruses at hospital admission and lower respiratory secretions were also obtained in intubated patients. Real-time polymerase chain reaction (PCR) testing was performed in accordance with the published guidelines from the Centers for Disease Control and Prevention.<sup>14</sup> A(H1N1) testing was performed in each institution or in a centralized reference laboratory when an institution was not available. A "confirmed case" was defined as an acute respiratory illness with laboratory-confirmed A(H1N1) virus infection identified by real-time PCR or viral culture.<sup>15</sup> Only confirmed cases were included in the current study.

CARC was defined as any infection diagnosed within the first 2 days of hospitalization. Infections occurring later were considered nosocomial.<sup>16</sup> The definition of hospital-acquired pneumoniae was based on current American Thoracic Society and Infectious Disease Society of America guidelines.<sup>17</sup> Patients who presented health-care-associated pneumonia were excluded from the study.<sup>17</sup> Patients were admitted to the ICU either because they were potential candidates for mechanical ventilation and/or because they were judged to be in an unstable condition requiring intensive medical or nursing care.<sup>18,19</sup>

For all patients, management for diagnosis was based on standardized guidelines<sup>20,21</sup> and Minister of Health specific protocols.<sup>22</sup> Blood samples for cultures and serologic studies were collected routinely at ICU admission. Paired serum samples were tested for evidence of complement fixation antibody to *Chlamydia* species, *Coxiella burnetii*, and *Mycoplasma pneumoniae*. The indirect fluorescent antibody technique was used to test for *Legionella pneumophila* serogroups. A urine enzyme-linked immunosorbent assay or immunochromatographic test was used to identify *L pneumophila* serogroup 1 or pneumococcal antigen. BAL was not performed because of the high risk of generating aerosols. A pleural effusion culture was performed in patients in whom pleural effusion was documented. Bacterial identification and susceptibility testing were performed by standard methods, based on local guidelines.

An organism was considered to be the definitive causative agent<sup>23</sup> only if it could be isolated from blood or pleural fluid. Other microorganisms isolated from quantitative endotracheal aspirate were considered "probable" pathogens.<sup>23</sup> Serologic tests revealing a fourfold increase in antibody levels were also considered as establishing a definitive diagnosis. The urinary antigen test for *Legionella* was interpreted by the presence of visually detectable pink-to-purple colored lines in 15 min, in which case the *Legionella* was considered probable. Definite diagnosis of aspergillosis was based on histopathologic samples and probable the presence of a halo or an air-crescent sign on a CT scan of the lung.<sup>24</sup>

Acute renal failure was defined as the need for renal replacement therapy, in accordance with the International Consensus Conference guidelines.<sup>25</sup> Oseltamivir was administered orally in accordance with Centers for Disease Control and Prevention recommendations, and the regimen (150 mg/24 h or 300 mg/24 h) was chosen by the attending physician.<sup>26</sup> The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation and type of antibiotic and antiviral therapy administered, were not standardized and were decided by the attending physician.

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Discrete variables are expressed as counts (percentage) and continuous variables as means  $\pm$  SD or medians with 25th to 75th interquartile range (IQR). For the demographic and clinical characteristics of the patients, differences between groups were assessed using the  $\chi^2$  test and the Fisher exact test for categorical variables and the Student *t* test or Mann-Whitney *U* test for continuous variables. Cox proportional hazards regression analysis was used to assess the impact of independent variables on ICU mortality across time. Variables significantly associated with mortality in the univariate analysis were entered in the model. To avoid spurious associations, variables entered in the regression models were those that showed a relationship in univariate analysis ( $P \leq .05$ ) or a plausible relationship with the dependent variable. Results are presented as hazard ratio (HR) and 95% CI. Potential explanatory variables were checked for collinearity prior to inclusion in the regression models using the tolerance and variance inflation factor. Data analysis was performed using SPSS for Windows, version 15.0 (SPSS, Inc; Chicago, Illinois).

## RESULTS

Six hundred forty-five ICU patients with A(H1N1) virus infection with severe respiratory failure in 148 hospitals in Spain were analyzed in this study. All patients were confirmed by real-time PCR for A(H1N1) and were being cared for in an ICU. Median days from symptoms onset to hospital admission and days from hospitalization to ICU admission were 4 and 1, respectively. Of these patients, 356 were men (55.2%) with a median age of 43 (IQR 34-54) years, and 555 (86%) were younger than 60 years. The mean APACHE II score was  $13.8 \pm 7.2$  and the mean SOFA score was  $5.6 \pm 3.6$  on admission. Comorbidities were present in 449 patients (69.6%). Obesity ( $n = 209$ ; 36.5%), COPD ( $n = 90$ ; 15.7%), and asthma ( $n = 70$ ; 12.2%) were the main comorbidities reported.

Primary viral pneumonia was documented in 354 patients (54.8%). In 113 patients (17.5%), another pathogen was isolated at ICU admission and patients were considered to have CARC. Quantitative endotracheal aspirate in 65.5%, urinary antigen in 23%, blood cultures in 6.2%, serology in 4.4%, and pleural fluid culture in 0.9% tested positive in the patients where CARC was documented. Postmortem studies were available in only 13 patients (2.3%). *S pneumoniae* in 62 patients (54.8%) was identified as the most prevalent bacteria, followed by *S aureus* in nine patients (8%). *Aspergillus* spp was identified from deep respiratory samples in 10 patients (8.8%), six presented halo or an air-crescent sign considered probable on CT scan, and two had confirmed lung histopathology (definite). Table 1 details the prevalence of pathogens isolated in patients with coinfection.

Patients with CARC were older ( $47.5 \pm 15.7$  vs  $43.8 \pm 14.2$  years,  $P < .05$ ) and presented a higher score on the APACHE II ( $16.1 \pm 7.3$  vs  $13.3 \pm 7.1$ ,  $P < .05$ ) and SOFA scores ( $7.0 \pm 3.8$  vs  $5.2 \pm 3.5$ ,

**Table 1—Pathogens Isolated in Patients With A(H1N1) Virus Infection With CARC**

Pathogens	No.	%	Definitive	Probable	Unproven
<i>Streptococcus pneumoniae</i>	62	54.8	6	56	...
<i>Aspergillus</i> sp	10	8.8	2 <sup>a</sup>	6 <sup>b</sup>	2
<i>Pseudomonas aeruginosa</i>	9	8.0	...	9	...
<i>Staphylococcus aureus</i> <sup>c</sup>	9	8.0	2	7	...
<i>Streptococcus pyogenes</i>	6	5.3	...	6	...
<i>Acinetobacter baumannii</i>	4	3.5	...	4	...
<i>Klebsiella pneumoniae</i>	4	3.5	...	4	...
<i>Haemophilus influenzae</i> / <i>Moraxella catarrhalis</i>	3	2.6	...	3	...
<i>Legionella pneumophila</i>	2	1.8	1	1	...
<i>Enterococcus faecium</i>	1	0.9	...	1	...
<i>Escherichia coli</i>	1	0.9	...	1	...
<i>Chlamydomphila pneumoniae</i>	1	0.9	1	...	...
<i>Mycoplasma pneumoniae</i>	1	0.9	1	...	...

A(H1N1) = pandemic 2009 influenza A(H1N1); CARC = community-acquired respiratory coinfection.

<sup>a</sup>Histopathologic confirmation.

<sup>b</sup>CT scan findings compatible with invasive *Aspergillus*.

<sup>c</sup>None methicillin-resistant *Staphylococcus aureus*.

$P < .05$ ) at admission. No differences in comorbidities were observed. Additional demographic data and clinical characteristics of patients with A(H1N1) with and without CARC are presented in Table 2. Table 3 displays the comparison of comorbidities for patients with or without CARC in the five pathogens more frequently isolated. No differences in comorbidities were observed except for *Aspergillus* spp, which was more frequently isolated in COPD patients.

Patients with CARC required vasopressors (63.7% vs 39.3%,  $P < .05$ ) and invasive mechanical ventilation (69% vs 58.5%,  $P < .05$ ) more frequently than those who did not present (Table 4). The incidence of hospital-acquired pneumoniae ( $n = 53$ , 9.1%) was not significantly different between the two groups (9.1% vs 9.2%,  $P = .9$ ). Length of ICU stay in survivors was 3 days longer in patients who had CARC compared with patients who did not (11 [IQR 5-23] vs 8 [IQR 4-17] days,  $P = .01$ ).

Empiric antiviral treatment was administered in 620 of the 645 patients (96.1%) and was less frequently administered in patients with CARC (97.0% vs 92.0%,  $P < .05$ ) and with a delayed administration ( $5.3 \pm 3.7$  vs  $4.5 \pm 2.7$   $P < .05$ ). Empiric antibiotic therapy was administered in all patients; however, empiric antifungal therapy was administered in only one patient who presented CARC with *Aspergillus* spp. CARC was associated with increased ICU mortality (26.2% vs 15.5%; OR, 1.94; 95% CI, 1.21-3.09); When ICU mortality was investigated according to pathogen, only *Aspergillus* spp was significantly associated with increased ICU mortality in the multivariate analysis (50.0% vs 18.4%; OR, 4.42; 95% CI, 1.26-15.54). A Cox



**Table 2—Comparison of Demographic and Clinical Characteristics Among Patients With A(H1N1) Virus Infection With or Without CARC**

Variables	Only A(H1N1) (n = 532)	Coinfection (n = 113)	P Value
Age, y	43.8 ± 14.2	47.58 ± 15.7	.01
Days from symptoms onset to hospital admission, median (IQR)	2 (4-5.75)	2 (4-5)	.9
Days from hospitalization to ICU admission, median (IQR)	1 (1-2)	1 (1-2)	.9
Male sex	287 (53.9)	69 (61.1%)	.1
APACHE II score	13.3 ± 7.1	16.1 ± 7.3	.001
SOFA score	5.2 ± 3.5	7.0 ± 3.8	.001
COPD	81 (15.2)	22 (19.5)	.2
Asthma	66 (12.4)	13 (11.5)	.8
CHF	38 (7.1)	8 (7.1)	.9
Chronic renal disease	26 (4.9)	2 (1.8)	.2
DM	64 (12.0)	13 (11.5)	.9
Obesity	108 (20.3)	20 (17.7)	.6
Autoimmune disorders	18 (3.4)	2 (1.8)	.5
Hematologic disease	33 (6.2)	7 (6.2)	.9
Neuromuscular disease	21 (3.9)	4 (3.5)	.9
HIV infection	12 (2.3)	5 (4.4)	.8

Data are presented as mean ± SD or No. (%), unless indicated otherwise. APACHE = Acute Physiology and Chronic Health Evaluation; CHF = chronic heart failure; DM = diabetes mellitus; IQR = interquartile range; SOFA = Sequential Organ Failure Assessment. See Table 1 legend for expansion of other abbreviations.

regression analysis adjusted by severity (APACHE II score) and the presence of comorbid conditions did not identify that coinfection was significantly associated with ICU mortality (HR, 1.18; 95% CI, 0.76-1.84;  $P = .45$ ) (Fig 1). Similar results were observed when adjusting for the most frequent pathogens isolated and when patients with *Aspergillus* spp isolation were excluded. In addition, early vs late differences in mortality were analyzed to evaluate the impact of 15-, 30-, and 60-day mortality, and no differences were noted (HR, 1.24, 95% CI, 0.72-2.13; HR, 1.16, 95% CI 0.72-1.87; HR, 1.19, 95% CI, 0.76-1.86, respectively).

## DISCUSSION

The main finding of this study is that the presence of CARC in patients hospitalized with a severe presentation of A(H1N1) was uncommon. *S pneumoniae* accounted for more than one-half of the episodes of coinfection. Although it was not associated with significantly increased mortality rates, coinfection was associated with longer and greater resource consumption, as defined by longer ICU stay.

The fatal outcome of A(H1N1) infection<sup>1-5</sup> is determined partly by the degree to which the influenza virus depresses local and general pulmonary defense mechanisms, and partly by the virulence and nature of the bacteria that invade the tissues in the wake of the specific virus. There is some controversy about the presence of coinfection and its association with severity. Although previous reports failed to prove such a correlation,<sup>27-29</sup> Palacios et al<sup>30</sup> studied swab samples from 199 patients affected by A(H1N1) and discovered an association with A(H1N1) severity of

illness and *S pneumoniae* CARC. Interestingly, the association with severity was not further explored with mortality. In our study, mortality was not increased in patients who presented with coinfection. This fact reinforces the role of the virus in causing critical illness and, as a consequence, the potential importance of pandemic vaccination.

In an analysis of lung tissue specimens from 77 confirmed fatal cases of A(H1N1) in the United States in which deaths occurred from May 1 to August 20, 2009, CARC was present in 22 cases (29%). Of the 22 cases with CARC, 10 were caused by *S pneumoniae*, seven by *S aureus*, six by *S pyogenes*, two by *Streptococcus mitis*, and one by *H influenzae*. In four cases there were multiple pathogens. These fatal cases were defined as influenza-like illness or by postmortem findings, suggesting viral pneumonia and laboratory-confirmed A(H1N1) by real-time reverse-transcriptase PCR. Nevertheless, this information should be evaluated cautiously because this report summarized cases that did not come from a systematic sample and might not be representative of all A(H1N1) deaths or all A(H1N1) deaths associated with bacterial pneumonia. Moreover, not all potential pathogens were evaluated, patient information was limited, and evaluation of coinfections was performed at autopsy. Our findings are similar to those in this report in terms of coinfection with common bacterial pathogens: *S pneumoniae* and *S aureus*. Additionally, group A streptococci are a rare but severe cause of community-acquired pneumonia<sup>31</sup> and have been associated with fatal cases of influenza.<sup>11</sup> In our series, group A streptococci represented 5.3% of the coinfections.

In our study, *S aureus* coinfection was present in 8% of patients and was the third most frequently

**Table 3—Comparison of Comorbidities and Mortality in Patients With A(H1N1) Virus Infection With CARC According to the Five Pathogens More Frequently Isolated**

Variables	<i>S pneumoniae</i> (n = 62)	<i>Aspergillus</i> sp (n = 10)	<i>S aureus</i> (n = 9)	<i>P aeruginosa</i> (n = 9)	<i>S pyogenes</i> (n = 6)
COPD	13 (21)	4 (40) <sup>a</sup>	0	2 (22.2)	1 (16.7)
Asthma	9 (14.5)	3 (30)	0	0	0
CHF	5 (8.1)	1 (10)	0	0	0
Chronic renal disease	1 (1.6)	0	0	1 (11.1)	0
DM	9 (14.5)	2 (20)	0	2 (22.2)	0
Obesity	9 (14.5)	4 (40)	1 (11.1)	1 (11.1)	0
Autoimmune disorders	1 (1.6)	0	0	0	0
Hematologic disease	5 (8.1)	1 (10)	0	0	0
Neuromuscular disease	3 (4.8)	0	0	1 (11.1)	0
HIV	3 (4.8)	1 (10)	0	0	1 (16.7)
ICU mortality	13 (21.0)	5 (50) <sup>a</sup>	1 (11.1)	4 (44.4)	2 (33.3)

Data are presented as No. (%). See Table 1 and 2 legends for expansion of abbreviations.

<sup>a</sup>*P* < .05.

isolated bacteria, but none was methicillin-resistant *S aureus* (MRSA). A retrospective study of influenza-related childhood deaths in the United States in the 2003-2004 season found *S aureus* to be the most common bacterial agent, accounting for 46% of isolates, >50% of which were MRSA.<sup>11</sup> Surveillance for severe influenza-related *S aureus* community-acquired pneumonia in the United States during the 2003-04 season recorded 17 cases (88% MRSA) and five deaths (four with MRSA), and a median age of 21 years<sup>32</sup>; laboratory evidence of influenza infection was available for ≈75%.

Interestingly, in 10 patients (two definite fatal infections), *Aspergillus* spp, and in nine patients, *Pseudomonas aeruginosa*, were isolated from deep respiratory samples. In the present study, patients with CARC were older. Ageing has been considered a contributor to CARC on the basis of deteriorated immune response. Despite the fact that mortality after day 20 seemed to split in the survival analysis, this difference was not statistically significant when adjusting for potential confounders, including age and comorbid conditions. This suggests that coinfection may be a marker for more vulnerable patients. In addition, determining the role played by the immune response in combating severe viral infections is not

easy, although understanding it is important for developing strategies for clinical management. Patients affected by A(H1N1) infection have an abnormal immune response. Bermejo-Martin et al<sup>33</sup> recently reported that severe A(H1N1) infection with respiratory involvement is characterized by an early secretion of Th17 and Th1 cytokines usually associated with cell-mediated immunity. Additionally, To et al<sup>34</sup> demonstrated a slower control of viral load and immunodysregulation (excessive cytokine activation) in patients with severe presentation (ARDS-death group) when compared with a mild-disease group. Bacteria, fungi, and viruses are all potential invaders in immunosuppressed patients. Moreover, fungal infection represents a significant cause of morbidity and mortality. The lifelong immunosuppression they undergo makes them vulnerable to nosocomial, endemic, and newly recognized fungal pathogens. Finally, the cause of the synergy between the influenza virus and CARC is poorly understood. Studies in animal models have proposed that pathologic changes were initiated by the infectious agents and regulated by host immune responses, including the Toll-like receptor-mediated signaling pathway. Concentrations of tumor necrosis factor- $\alpha$ , IL-6, macrophage inflammatory protein 2 (functionally similar to IL-8 in humans), and regulated on activation, normal T expressed and secreted increased significantly in the lungs of coinfecting animals.<sup>35</sup>

In our series, an association with *Aspergillus* spp coinfection and COPD was observed. The role of such pathogens in COPD patients has been documented previously, with one result an increased mortality.<sup>36</sup> Invasive *Aspergillus* infection is extremely rare in the presence of normal immunity. Patients with COPD may be at risk of developing pulmonary *Aspergillus* infection. In the present study, only one patient who presented with CARC with *Aspergillus* spp received empiric antifungal therapy. Therefore, CARC with *Aspergillus* spp should be considered a diagnostic

**Table 4—Initial Treatment Among Patients With A(H1N1) Virus Infection With or Without CARC**

Variables	Only A(H1N1) (n = 532)	Coinfection (n = 113)	<i>P</i> Value
Invasive mechanical ventilation	311 (58.5)	78 (69.0)	< .05
Vasopressor drugs	209 (39.3)	72 (63.7)	< .01
Hemofiltration	33 (6.2)	12 (10.6)	.1
Dialysis	13 (2.4)	6 (5.3)	.1
Prone positioning	70 (13.2)	14 (12.4)	.9
Corticosteroids	220 (41.4)	47 (41.6)	.9

Data are presented as No. (%). See Table 1 legend for expansion of abbreviations.

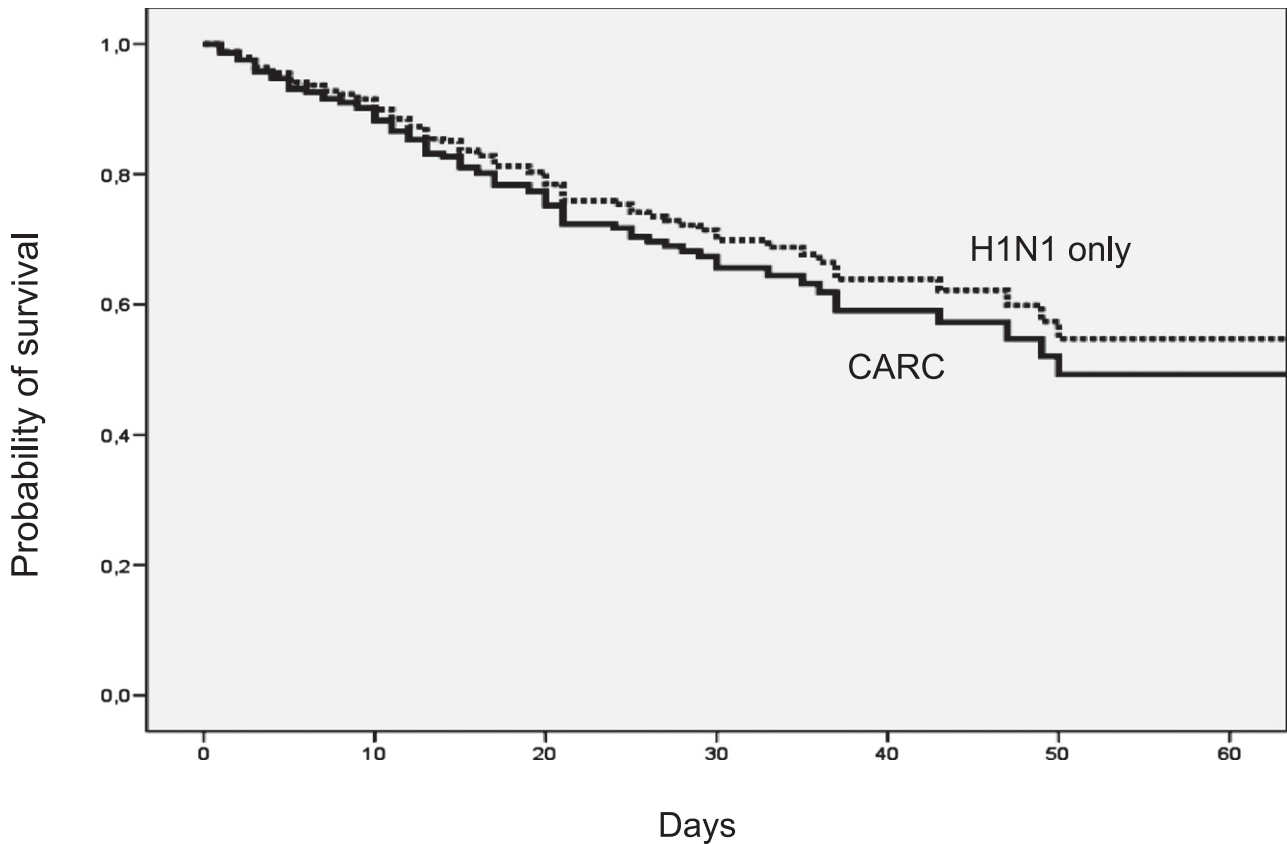


FIGURE 1. Cox regression analysis for patients who presented or did not present with community-acquired respiratory coinfection and were infected with pandemic 2009 influenza A(H1N1). (Censored at 60 days.) H1N1 = pandemic 2009 influenza A(H1N1); CARC = community-acquired respiratory coinfection.

possibility in patients with nonresolving A(H1N1). Nevertheless, because the diagnosis of definitive invasive aspergillosis requires histopathologic confirmation, further investigation should be carried out to determine the exact impact of such pathogens.

The present study has several potential limitations that should be addressed. First, this was an observational, noninterventional study in which detailed causes of death were not recorded. Second, the diagnosis of viral infection was based on nasopharyngeal-swab where the determination of viral load measurement was not performed. It has been reported that nasal PCR can remain positive for weeks after clinical resolution of A(H1N1). Because viral lung infection was not documented, we cannot really be sure which episodes were coinfection and which were bacterial infection following an earlier A(H1N1) infection. However, within the 8 weeks' peak of the 2009 pandemic, most patients' clinical presentation, CT scans, and biomarkers (eg, lactate dehydrogenase), were all consistent with viral pneumonia. Third, only adults admitted to Spanish ICUs were included; therefore, our results might not be generalized to other countries or to children.

Prescription practices were chosen in accordance with local protocols. Similarly, techniques of pathogen

identification, including aspergillosis, were not standardized, and were mainly based on tracheal aspirate obtained immediately after intubation rather than on invasive techniques. During the 2009 pandemic, BAL was not performed systematically because of the high risk of generating aerosols. The use of bronchoscopic lavage, protected specimen brushing, or *trans*-bronchial or *trans*-thoracic lung biopsies have potential risks in severe hypoxemic intubated patients and are uncommon for standard management of patients with severe community-acquired pneumonia.<sup>17,37</sup> Nevertheless, such invasive techniques are indicated in superinfections or nonresolving pneumonia.<sup>38</sup> In addition, the implementation of postmortem studies was marginally implemented; therefore, definitive diagnosis for *Aspergillus* spp was confirmed in two patients. Finally, the isolation of other types of influenza viruses was not investigated, but during the present pandemic, 99% were influenza A: 0.03% influenza A(H1); 0.07% A(H1N1); 0.125 influenza A(H3); 0.3% influenza A(H3N2), and 99% A(H1N1); the other influenza viruses were 1.2% influenza B and 0.09% influenza C.<sup>39</sup> Several authors<sup>40</sup> have reported the presence of a lethal synergism between seasonal influenza virus and *S pneumoniae*, which likely

accounts for excess mortality from secondary bacterial pneumonia during influenza epidemics. This effect was specific for viral infection preceding bacterial infection. This was not shown in the present study.

## CONCLUSIONS

In summary, we report that CARC was uncommon among patients with A(H1N1) in the ICU. We documented a statistically significant association between bacterial coinfection and higher health-care resources consumption, but there was not a statistically significant association between bacterial coinfection and ICU mortality. Whereas *S pneumoniae* was present in more than one-half of coinfection episodes, suggesting that they would be prevented by widespread pneumococcal vaccination, our findings reinforce the role of the virus in causing critical illness.

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*Dr Sanchez-Corral:* contributed to data acquisition, analysis, and approval of the final version of the article.

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## Community-Acquired Respiratory Coinfection in Critically Ill Patients Infected With Pandemic 2009 Influenza A(H1N1) Virus Infection

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