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EDITORIAL

Co-infection in severe influenza: a new epidemiology?

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In 2009, a novel influenza A (H1N1) virus emerged in Mexico and caused human infection, including severe pneumonia in young and previously healthy adults [1]. Since 2009, the virus has continued to circulate, causing cases of viral pneumonia and acute respiratory distress syndrome requiring intensive care unit (ICU) admission. Other serotypes [influenza B, A (H3N2)] circulate concomitantly and are also responsible for cases of severe acute illness requiring ICU admission [2]. Although primary viral pneumonia may evolve towards acute respiratory distress syndrome and death, bacterial co-infection is frequently described in these cases, may contribute to the development of ARDS and respiratory failure, and is clearly associated with higher mortality [1, 3].

In a study described in a recent article in *Intensive Care Medicine*, Martin-Loeches at al., investigated 2901 patients with influenza infection hospitalized in 148 Spanish ICUs from 2009 to 2015 and found that 16.6% of them had microbiologically confirmed community-acquired co-infection (i.e., co-infection diagnosed within the first 2 days of hospital admission) [4]. Similar to previously reported data from this group [5], *Streptococcus pneumoniae* was the predominant pathogen recovered, followed by *Pseudomonas aeruginosa* and methicillin-susceptible *Staphylococcus aureus* (MSSA). Not unexpectedly, data from the USA found that *S. aureus* was the predominant organism, with a higher prevalence of methicillin-resistant *S. aureus* (MRSA) [6]. Interestingly, the authors found an apparent increased rate of co-infection over time (from 11.4% in 2009 to 23.4% in 2015), without clear explanation. A recent meta-analysis showed that co-infection rates ranged from 2 to 65% [7]. This difference between studies could be explained by differences in methods of sampling, timing of samples, prehospital antibiotic administration, and different definitions of co-infection (i.e., whether or not it was microbiologically confirmed, etc.). In the study by Martin-Loeches at al., it is difficult to draw conclusions on the exact incidence of co-infection and its increase over time: firstly, the definition of co-infection required laboratory confirmation and the study did not record the proportion of patients having received antimicrobials before hospital admission (which would decrease the ability to confirm co-infection in the laboratory and can vary over time); and secondly, as a result of the use of non-invasive techniques, namely tracheal aspirate, for diagnosing pneumonia, the authors might have missed some cases that would only be laboratory confirmed by more invasive sampling (i.e., bronchoscopy). Furthermore, they could have classified patients as having co-infection whereas they were only colonized [8]. This potential overestimation could also explain the high rate of *P. aeruginosa* co-infection observed in that study (14.1%): in another recent study in patients with influenza-related infection, the authors found a 1.3% rate of *P. aeruginosa* co-infection in patients with CAP and 8.3% in patients with healthcare-associated pneumonia (HCAP) [9]. The high incidence found in the present study cannot be explained by a local (national) feature, since same authors reported lower rates of *P. aeruginosa* CAP and HCAP in Spain during this same time [10, 11]. Either false positives (patients diagnosed as pneumonia whereas only colonized) or a specific, not yet described, influenza–*P. aeruginosa* co-infection (Shah at al., found similar incidence of *P. aeruginosa* [12]) could explain such high rates of *P. aeruginosa* pneumonia, especially if they truly are community acquired. The high rate of co-infection due to *Aspergillus* (7.2%) is also surprising: although invasive pulmonary aspergillosis has been described in patients with H1N1-related pneumonia, it has rarely been

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described as a community-acquired co-infection but more as a secondary fungal infection, even in immunosuppressed patients [13, 14]. Although this study focused on community-acquired co-infection (and in fact excluded patients admitted from nursing homes or other healthcare facilities), the high incidences of *P. aeruginosa* and *Aspergillus* as pathogens responsible for co-infection is in favor of a mix of community-acquired infections and secondary bacterial and fungal infections.

Another surprising result of this paper is the absence of association between appropriate use of antibiotics and mortality, since this has been demonstrated years ago [15]. However, this could be explained not (only) by an unknown and complex host–pathogen interaction, as stated by the authors, but by the high reported rate of inappropriate empiric therapy (>15%) that was similar in survivors and non-survivors [4]. The particular epidemiology of pathogens responsible for co-infection, specifically the higher than expected rates of *P. aeruginosa* and *Aspergillus*, may explain this finding.

Some important messages should be taken from this paper, as the winter is near in the northern hemisphere and we will soon probably face new cases of influenza-related illness requiring ICU admission. First, co-infection is frequent in patients with influenza infection. Physicians taking care of these patients should strongly consider whether their critically ill influenza patient may be co-infected, and empirically treat with antibiotics. Second, co-infection is associated with higher mortality rate than primary viral infection. Although this was previously demonstrated in several studies, this is the largest study published to date that confirms this association. Rice at al., found, in 2012, that among 683 patients with influenza A H1N1 infection, bacterial co-infection was frequent (30.3%) and associated with higher mortality rate as compared to patients without [6]. In a more recent study on 507 ICU patients, Shah at al., found a 22.5% rate of bacterial co-infection and a similar association between bacterial co-infection and death [12]. It is highly probable that the mechanism explaining the higher mortality is due to either to the bacterial infection itself or to an association of virulence factors from both virus and bacteria. Lastly, as shown in this paper and others, the epidemiology of pathogens responsible for co-infection is regional and likely depends on many local factors, but may also be subject to change over time, with emergence in the community of pathogens usually seen in nosocomial infections [6, 7, 9, 12].

These and previous data on co-infection rates and association with higher mortality beg the question of whether every patient with severe influenza should be treated with antibiotics? Unfortunately this paper does not give the answer to this crucial question, but the answer may very well be an emphatic "Yes". Given the high probability of bacterial co-infection in these patients, its association with mortality, and the fact that delaying antimicrobial treatment could be associated with even higher mortality [16], the empiric use of antimicrobial treatment in such patients should be encouraged. Although some biomarkers (and in particular procalcitonin) have been shown to be associated with bacterial co-infection in this setting, their accuracy is not sufficient to determine initiation of antimicrobial treatment [17]. Procalcitonin may be helpful in this setting as a marker to stop antimicrobial treatment in patients without proven infection and/or low procalcitonin level [18].

In summary, clinicians should keep in mind that co-infection is frequent in patients with influenza-related infection requiring ICU admission. Thus, empiric antimicrobial treatment should be started early. The choice of the initial antimicrobial treatment should be based on the local and national epidemiology and target pathogens responsible for CAP: in France and northern Europe, *S. pneumoniae* and methicillin-susceptible *S. aureus* seem to be the predominant pathogens. In the USA, the high incidence of methicillin-resistant *S. aureus* should be taken into account for the initial choice of antibiotics [6]. If *P. aeruginosa* incidence is increasing over time (which remains to be confirmed in further studies), it may also need empiric antimicrobial coverage since it may have an impact on overall mortality.

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ORIGINAL

Increased incidence of co-infection in critically ill patients with influenza

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Abstract

Background: Co-infection is frequently seen in critically ill patients with influenza, although the exact rate is unknown. We determined the rate of co-infection, the risk factors and the outcomes associated with co-infection in critically ill patients with influenza over a 7-year period in 148 Spanish intensive care units (ICUs).

Methods: This was a prospective, observational, multicentre study. Influenza was diagnosed using the polymerase chain reaction. Co-infection had to be confirmed using standard bacteriological tests. The primary endpoint of this analysis was the presence of community-acquired co-infection, with secondary endpoints including ICU, 28-day and hospital mortality.

Results: Of 2901 ICU patients diagnosed with influenza, 482 (16.6 %) had a co-infection. The proportion of cases of co-infection increased from 11.4 % (110/968) in 2009 to 23.4 % (80/342) in 2015 ($P < 0.001$). Compared with patients without co-infection, patients with co-infection were older [adjusted odds ratio (aOR) 1.1, 95 % confidence interval 1.1–1.2; $P < 0.001$] and were more frequently immunosuppressed due to existing HIV infection (aOR 2.6 [1.5–4.5]; $P < 0.001$) or preceding medication (aOR 1.4 [1.1–1.9]; $P = 0.03$). Co-infection was an independent risk factor for ICU mortality (aOR 1.4 [1.1–1.8]; $P < 0.02$), 28-day mortality (aOR 1.3 [1.1–1.7]; $P = 0.04$) and hospital mortality (aOR 1.9 [1.5–2.5]; $P < 0.001$).

Conclusions: Co-infection in critically ill patients with influenza has increased in recent years. In this Spanish cohort, age and immunosuppression were risk factors for co-infection, and co-infection was an independent risk factor for ICU, 28-day and hospital mortality.

Keywords: Influenza, Co-infection, Risk factors, Outcome, Intensive care

Introduction

Severe acute respiratory infection with H1N1 influenza emerged in 2009 and was associated with high mortality rates [1]. The use of early antiviral therapy was one of the cornerstones of treatment in severe respiratory infection with influenza, and was associated with better outcomes. Many patients were suspected of having a community-acquired co-infection [2]. Therefore, it was recommended to consider antibacterial treatment on admission, until an accompanying bacterial infection was excluded [3].

Previous studies suggested temporal relationships between influenza and co-infection [4]. Indeed, retrospective analysis of lung biopsies of patients who died from influenza in the pandemic of 1918 suggested bacterial super-infections of the lungs [5]. This was also found for the influenza pandemic in 1957 [6]. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are the most-cited bacterial causes of co-infection.

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Take-home message: Based on the data presented, co-infection is a very frequent complication in critically ill patients with influenza. Streptococcus pneumoniae is still the most frequent pathogen with higher rates of potentially resistant pathogens. Immunosuppression is a risk factor for co-infection.

H1N1 SEMICYUC Working Groupinvestigators are listed in Appendix section .

However, *Aspergillus* spp. have also been identified as important pathogens [7]. The exact rate of co-infection and its risk factors, however, remained largely unknown. There is also a lack of understanding of the potential impact of co-infection on the outcome of patients with influenza [8].

We hypothesized that community-acquired co-infection is common and independently associated with mortality in intensive care unit (ICU) patients with influenza. Therefore, we reanalysed the data of a prospective observational study on influenza in critically ill patients in Spain from 2009 to 2015, covering four influenza seasons. In addition, we determined risk factors for co-infection.

Patients and methods

Study design

This was a prospective, observational study conducted from 2009 to 2015 in a large cohort of ICUs in Spain. There were four seasons of influenza, based on epidemic threshold rates developed by the Spanish Ministry of Health [9]: one in 2009 during the influenza H1N1 pandemic, one in the winter of 2010 to 2011, one in the winter of 2014, and one in the winter of 2015. During these four seasons (2009, 2010, 2014 and 2015), all patients admitted to the ICU with influenza-like symptoms were systematically tested to confirm respiratory infection with influenza A or bacterial pathogens. Local investigators registered data of consecutive influenza patients in a national registry created by the Spanish Society of Intensive Care Medicine. The institutional review board of Joan XXIII University Hospital approved the original study (IRBref#11,809) and waived the requirement for patients to give individual informed consent due to the observational nature of the study. The participation of 148 ICUs meant that we could monitor and prospectively follow approximately 80 % of the patients admitted to Spanish ICUs with influenza.

Inclusion and exclusion criteria

This reanalysis did not use inclusion or exclusion criteria other than those employed in the original study. However, patients under the age of 16 years and patients admitted from nursing homes or other healthcare facilities were excluded.

Standard care and collection of samples for diagnostic purposes

The Ministry of Health and competent authorities in Spain intensively monitored and audited management of influenza in the national ICUs. Standardized guidelines were used in all centres [10]. Oseltamivir therapy was considered early treatment (ET) if administered within 2 days of the onset of influenza symptoms [2], and empirical antibiotics were started after obtaining a nasopharyngeal swab, endotracheal aspirates and blood. Nasopharyngeal swabs were used for viral testing, respiratory secretions for quantitative cultures, and blood samples were cultured and used for serological tests. Bronchoalveolar lavage fluids were not obtained because of the high risk of generating aerosols. If present, pleural effusions were punctured for microbiological culture.

Definitions

Co-infection was suspected if a patient had an acute onset of signs and symptoms suggesting lower respiratory tract infection, with radiographic evidence of a pulmonary infiltrate that had no other known cause [11]. Co-infection had to be laboratory confirmed using the Centers for Disease Control and Prevention criteria. If the co-infection was diagnosed within 2 days of hospital admission, it was considered a community-acquired co-infection. The diagnosis was considered definitive if respiratory pathogens were isolated from blood or pleural fluid and if serological tests confirmed a fourfold increase of atypical pathogens, including *Chlamydia* spp., *Coxiella burnetii* and *Moraxella pneumoniae*. Respiratory aspergillosis was considered a 'definite' diagnosis only if *Aspergillus* spp. were identified on histopathology. The diagnosis was considered 'probable' if respiratory pathogens were isolated in endotracheal aspirates. Respiratory aspergillosis was considered a 'probable' diagnosis in the presence of halo or air-crescent signs on computed tomography of the lungs with positive determination of serum galactomannan, and 'possible' if *Aspergillus* spp. were found in endotracheal aspirates [7]. Appropriateness of antibiotic therapy was defined as administration of at least one antimicrobial agent effective against the isolated pathogen.

Study endpoints

The primary endpoint of this analysis was the presence of community-acquired co-infection. Secondary endpoints included ICU, 28-day and hospital mortality, the number of ventilator-free days and patient's survival at day 28. Ventilator-free days were defined as days of successful and complete weaning from mechanical ventilation up to day 28. For subjects who died during this period, the ventilator-free days were counted as 0 [12].

Analysis plan

Firstly, the proportion of cases and rate of co-infection were determined. This rate was calculated per season and comparisons made among seasons. The first season acted as reference season, and calculations were carried out using logistic regression and odds ratios with confidence intervals. This was repeated for each pathogen.

Associations between co-infection and the clinical outcome measures were studied by logistic regression and corrected for potential confounders, which included gender, age, disease severity (APACHE II

score), comorbidities (asthma, chronic obstructive pulmonary disease, chronic heart failure, chronic kidney disease, haematological disease, diabetes mellitus, HIV and immunodeficiency), pregnancy, obesity, oseltamivir treatment, appropriateness of initial antibiotic therapy, acute kidney injury, need for renal replacement therapy, need for invasive mechanical ventilation and presence of septic shock. Potential chronic comorbidities and states that were risk factors for the occurrence of co-infection included asthma, chronic obstructive pulmonary disease, pregnancy, obesity, diabetes mellitus, HIV and immunodeficiency and were also identified by logistic regression. Both analyses started with all potential confounders and backward selection based on *P* value was performed.

Statistical analysis

Discrete variables are expressed as counts with percentage and continuous variables, as means and standard deviation (SD) or as medians with the 25th to 75th interquartile range (IQR). Parametric or nonparametric tests were used for continuous variables as appropriate after the normality of the distribution had been tested. A *P* value <0.05 was considered significant. Differences in patients' demographic and clinical characteristics were assessed using the Chi squared test or Fisher's exact test for categorical variables and Student's *t* test or the Mann–Whitney *U* test for continuous and ordinal variables, where appropriate.

Trends in the rate and proportion of cases of co-infection and causative pathogens were assessed by logistic regression, with 2009 selected as the year of reference. A stepwise backward-selection logistic regression analysis was performed to study the association with outcome. Variable selection was done based on *P* values (<0.10). For all models that had ICU mortality as the dependent variable, the APACHE II score was included as covariate, irrespective of the associated *P* value. Potential explanatory variables were checked for co-linearity prior to inclusion in the regression models using tolerance and variance inflation factor.

All statistical analysis was performed using SPSS v.20.0 for Mac (IBM Corp., Armonk, NY, USA).

Results

Patients

A total of 2901 ICU patients with polymerase chain reaction (PCR)-confirmed influenza were included and analysed (Table 1; Fig. 1); 1581 patients were male (59.1 %) and the mean age was 51.6 ± 15.9 years. All patients were severely ill, with a mean APACHE II score of 16.1 ± 7.6. The mean ICU and hospital length of stay were 13.5 ± 14.6 and 21.4 ± 18.8 days, respectively. ICU mortality, 28-day mortality and hospital mortality were 22.1, 19.7 and 26.2 %, respectively. *S. pneumoniae* was the bacterium most often identified, followed by *Pseudomonas aeruginosa* and methicillin-sensitive *S. aureus* (MSSA) (Table 2).

Table 1 Characteristics of patients included in the study (N = 2901)

Variable	n = 2901
Sex (male) (n, %)	1706, 59.1 %
Age (mean ± SD)	51.6 ± 15.9
APACHE II score (mean ± SD)	16.1 ± 7.6
Asthma (n, %)	291, 10.1 %
Chronic obstructive pulmonary disease (n, %)	608, 21.2 %
Chronic heart failure (n, %)	331, 11.5 %
Chronic kidney disease (n, %)	246, 8.6 %
Haematological diseases (n, %)	197, 6.9 %
Pregnancy (n, %)	109, 3.8 %
Obesity (n, %)	962, 33.5 %
Obesity (BMI > 40) (n, %)	406, 14.1 %
Diabetes mellitus (n, %)	477, 16.6 %
HIV (n, %)	70, 2.4 %
Immunodeficiency (n, %)	311, 10.8 %

Relative rate of co-infection

Overall, co-infection was diagnosed in 16.6 % of patients. An increasing trend was observed over the years of the study: 11.4 % in 2009, 17.3 % in 2010, 18.8 % in 2014, and as high as 23.4 % in 2015. The odds ratios (OR) for co-infection were 1.6 [1.2–2.2], 1.8 [1.4–2.4] and 2.4 [1.7–3.3] in 2010, 2014 and 2015 respectively (Fig. 2). A significant increase in the rates of *S. pneumoniae*, *P. aeruginosa*, MSSA and *H. influenzae* co-infection over the years was found (Fig. 2). The relative frequency of *Aspergillus* spp. did not increase over the years of the study (Fig. 2).

Risk factors for co-infection

Comorbidities in patients with and without co-infection are shown in Table 3. The likelihood of co-infection increased with age (adjusted OR 1.01 [1.01–1.02]), preceding HIV infection (adjusted OR 2.6 [1.5–4.5]) and immunosuppressive medication (adjusted OR 1.4 [1.02–1.9]). The numbers of days from onset of clinical symptoms to hospital admission, from hospital admission to start of antiviral therapy, and from onset of clinical symptoms to start of antiviral therapy did not differ between patients with and without co-infection (Supplementary Table 1) (Fig. 3).

Clinical outcomes

ICU mortality was not significantly different among influenza types (A-H1N1: 21.9 %; A-H3N2: 24.2 %; B: 18.9 %;

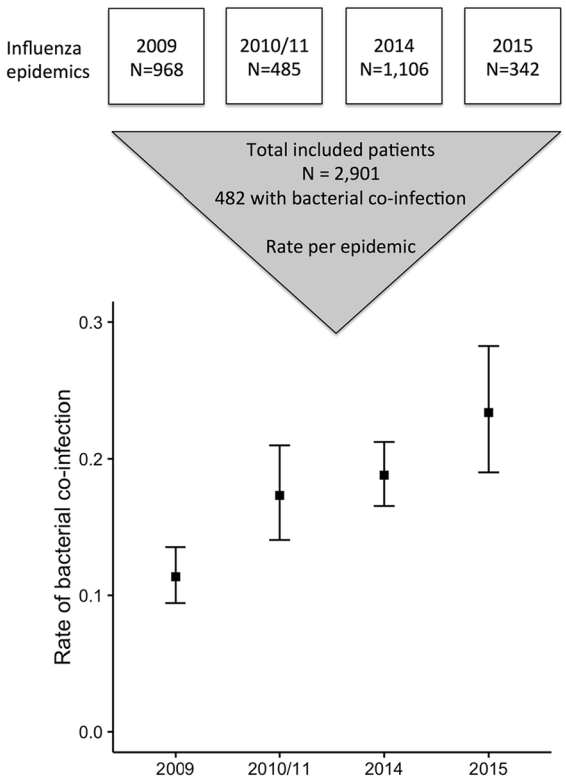

Fig. 1 Inclusion diagram and rate of bacterial co-infection per epidemic period. Patients from four influenza epidemics were included. The total number of patients with a positive PCR for influenza was 2901. Of these, 482 had a bacterial co-infection. The *lower panel* gives the rate of co-infection in each period. The *error bars* indicate the 95 % confidence interval

Table 2 Numbers and proportions of the pathogens isolated in critically ill patients with bacterial co-infection (N = 482)

Pathogen	N	%+	Definitive	Probable	Possible
S. pneumoniae	246	51.04	17	229	0
P. aeruginosa	55	11.4	2	53	0
MSSA	42	8.7	2	40	0
Aspergillus spp.	35	7.2	2*	25**	8
H. influenza	17	3.5	0	17	0
A. baumannii	14	2.9	0	14	0
MRSA	12	2.4	3	9	0
K. pneumoniae	12	2.4	1	11	0
E. coli	11	2.2	1	10	0
L. pneumophila	5	1.1	1	4	0
S. marcescens	4	0.8	1	3	0
S. hominis	4	0.8	4	0	0
E. cloacae	4	0.8	2	2	0
P. jirovecii	4	0.8	0	4	0
M. pneumoniae	4	0.8	1	3	0
C. pneumoniae	3	0.6	1	2	0
M. tuberculosis	3	0.6	0	3	0
S. maltophila	2	0.4	0	2	0
K. oxytoca	2	0.4	0	2	0
M. morganii	1	0.2	0	1	0
Shewanella spp.	1	0.2	0	1	0
B. fragilis	1	0.2	0	1	0
Nocardia spp.	1	0.2	0	1	0

MRSA methicillin-resistant *Staphylococcus aureus, MSSA* methicillin-sensitive *Staphylococcus aureus*

* Histopathological confirmation

** CT findings compatible with invasive aspergillosis

+ Percentage of all microorganisms

C: 18.8 %; $P = 0.7$) for patients with or without co-infection. Patients with co-infection more often received early oseltamivir treatment than those without co-infection (1428/2419, 59 % vs. 314/482, 65.1 %; $P = 0.01$). However, early oseltamivir treatment was not associated with a significantly lower ICU mortality in patients with (171/259; 66.6 vs. 122/192; 63.5 %; $P = 0.6$) or without co-infection (1187/1982; 59.9 vs. 419/702; 59.7 %; $P = 0.9$),. Continuous renal replacement therapy, invasive mechanical ventilation and immunosuppression were independently associated with ICU mortality; the adjusted OR (aOR) values are summarized in Table 4. Co-infection was also independently associated with increased ICU mortality (aOR 1.4, 95 % CI 1.1–1.8; $P < 0.02$; Table 4), 28-day mortality (aOR 1.3, 95 % CI 1.1–1.7; $P = 0.04$) and hospital mortality (aOR 1.9 95 % CI 1.5–2.5; $P < 0.001$). The mean number of ventilator-free days and survival at day 28 were lower in patients with co-infection (12.9, IQR 10.6–14.2 vs. 10.3, IQR 9.6–12.1; $P < 0.001$). A subgroup analysis showed that only positive cultures for *P. aeruginosa* (aOR 2.6, 95 % CI 1.3–5.1; $P = 0.004$) or *Aspergillus* spp. (aOR 4.1, 95 % CI 1.9–9.6; $P = 0.001$) were independent risk factors for ICU mortality when corrected for APACHE II score.

Discussion

We have reported data from the largest prospective study to date evaluating patients with severe influenza admitted to the ICU. The most significant finding was the high rate of co-infection, complicating the clinical course in one out of six critically ill patients with influenza. Moreover, the rate of co-infection steadily increased over the study period and was independently associated with increased mortality.

Previous studies have provided conflicting results regarding the impact of co-infection on patient outcome. For example, a study performed in Europe, identifying *S. pneumoniae* as the most frequent pathogen isolated in co-infection, demonstrated no significant association between co-infection and ICU mortality after adjustment

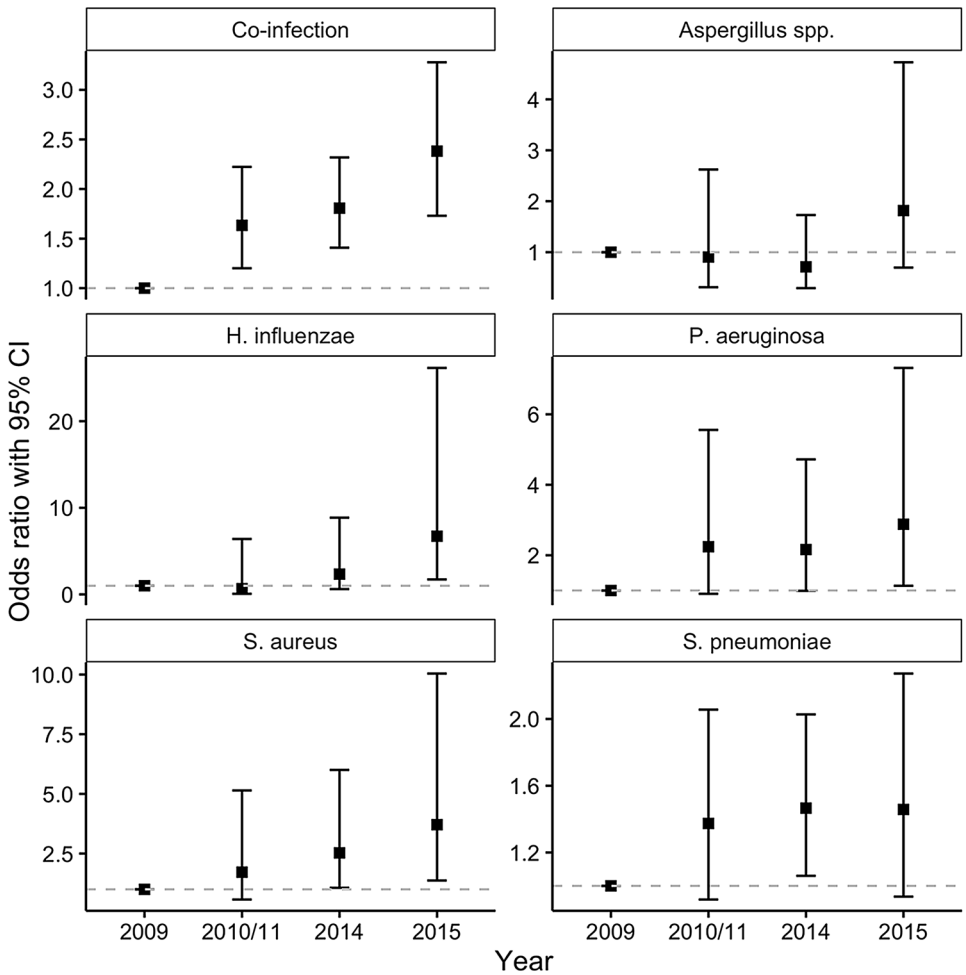

Fig. 2 Odds ratios for co-infection, stratified by pathogen. Odds ratio and 95 % confidence intervals are shown per epidemic period for all co-infection (*upper left*) and per pathogen. The *dotted line* indicates an odds ratio of 1. If the *error bars* cross this line, the rate is not significantly different from the rate in 2009, the reference year

for confounding factors [13]. In contrast, a retrospective study analysing 683 critically ill patients in the USA with confirmed or probable 2009 influenza A, found that bacterial co-infection, especially with *S. aureus*, was associated with significantly higher mortality [14]. The main differences between these studies were that in the USA study only 62.1 % of the patients had confirmed co-infection and there was a higher rate of *S. aureus*.

All the studies published to date in critically ill patients have focused on only one influenza season, the vast majority of them on the 2009–2010 pandemic season [14–19]. Some studies also attempted to analyse the occurrence and impact of bacterial organisms complicating critical care illness during the previous 12 months [20]. In the current study we present the clinical characteristics and trend of co-infection over the past 7 years (2009–2015), providing useful information for the management of patients with severe influenza.

Studies analysing the frequency of influenza and bacterial co-infection have reported high heterogeneity. A recent systematic review and meta-analysis of 27 studies analysed the frequency of bacterial co-infection in influenza patients. The results from these studies were highly variable, ranging from 2 to 65 %, although the majority of studies ranged between 11 and 35 % [21]. Our results show a significant increase in occurrence from 11.4 % in 2009 to 23.4 % in 2015. The most frequent pathogen identified in the seven-year period was *S. pneumoniae* followed by *P. aeruginosa* and MSSA. In the last few years the rate of isolation of *S. pneumoniae* has been declining and the rates of *P. aeruginosa* and *H. influenzae* have increased. It is worth mentioning the reappearance of

Table 3 Unadjusted and adjusted risk factors for co-infection in critically ill patients with confirmed influenza infection

Variable	Co-infection					Adjusted OR	
	No N = 2233		Yes N = 451		*P* value	OR (95 % CI)	*P* value
Sex (male) (n, %)	1399	58.1 %	307	63.8 %	0.04		
Age (mean, SD)	51.1	14.9	55.4	16.0	<0.001	1.1 (1.1–1.2)	<0.001
Asthma (n, %)	249	10.4 %	42	8.8 %	0.3		
Chronic obstructive pulmonary disease (n, %)	494	20.6 %	114	23.8 %	0.1		
Chronic heart failure (n, %)	281	11.7 %	50	10.5 %	0.4		
Chronic kidney disease (n, %)	202	8.4 %	44	9.2 %	0.5		
Haematological diseases (n, %)	2234	93.3 %	441	92.3 %	0.4		
Pregnancy (n, %)	102	4.3 %	7	1.5 %	0.02		
Obesity (n, %)	840	35.1 %	122	25.5 %	0.01		
Obesity > 40 BMI (n, %)	358	15.0 %	48	10.0 %	0.04		
Diabetes mellitus (n, %)	401	16.8 %	76	15.9 %	<0.001		
HIV (n, %)	47	2.0 %	23	4.8 %	<0.001	2.6 (1.5–4.5)	0.001
Immunodeficiency (n, %)	243	10.2 %	68	14.2 %	0.01	1.4 (1.1–1.9)	0.03

The multivariate model included age, gender, APACHE II score, asthma, chronic obstructive pulmonary disease, pregnancy, obesity, diabetes mellitus, HIV and immunodeficiency as eligible variables. Backward selection based on *P* value was used to obtain the optimal model

HIV human immunodeficiency virus

methicillin-resistant *S. aureus* (MRSA). When we analysed results for each pathogen individually, we found that co-infection with MSSA, *P. aeruginosa* and *Aspergillus* spp. was associated with significant mortality. These changes in epidemiology over the years may explain why, as shown in our study, co-infection has become an independent risk factor for ICU mortality.

In general, patients presenting with co-infection in our study were older, had more comorbidities (obesity, HIV and immunosuppression) and a higher severity of illness (APACHE and SOFA scores). Whilst HIV and immunosuppression were not identified as independent risk factors for co-infection in previous studies, our data show that these variables were not only associated with an increased rate of co-infection, but were also identified as risk factors for mortality in the post-pandemic period. [1, 22]. In terms of severity, patients with co-infection presented more organ failure (acute kidney injury, need for mechanical ventilation and shock). After adjusting for potentially confounding variables, the presence of co-infection was a risk factor independently associated with mortality. One important finding was the low rate of patients (4 %) with *S. pneumoniae* co-infection and a bacteraemic episode. Whilst the rate has commonly been reported as above 20 % in patients with community-acquired pneumonia, large multicentre studies [23] have also shown low rates (9.2 %). Bacteraemic episodes are associated with a higher fatality rate, and as a result, reports of bacteraemic episodes in patients with influenza have been less closely studied. This warrants further investigation to determine the virulence by comparing rates of bacteraemic episodes in patients with community-acquired pneumonia with and without influenza.

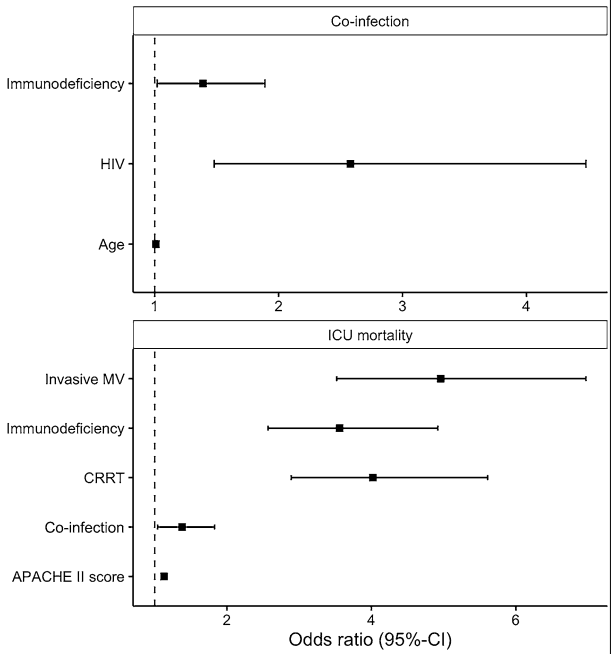

Fig. 3 Adjusted odds ratios for risk factors associated with ICU mortality

The delayed administration of antiviral treatment has been reported as a risk factor for ICU mortality [24]. In

Table 4 Unadjusted and adjusted ICU mortality by risk factors of critically ill patients with confirmed influenza infection for ICU mortality

Variable	ICU mortality					Adjusted OR	
	No N = 2091		Yes N = 593		*P* value	OR (95 % CI)	*P* value
Sex (male) (n, %)	1200	57.6 %	381	64.2 %	0.04		
Age (mean, SD)	50.5	15.7	55.6	16.1	<0.001		
APACHE II score (mean, SD)	14.6	6.7	21.06	8.4	<0.001	1.1 (1.1–1.2)	<0.001
Asthma (n, %)	234	11.3 %	42	7.1 %	0.003		
Chronic obstructive pulmonary disease (n, %)	442	21.3 %	121	20.6 %	0.7		
Chronic heart failure (n, %)	222	10.7 %	89	15.1 %	0.04		
Chronic kidney disease (n, %)	143	6.9 %	82	13.9 %	<0.001		
Haematological disease (n, %)	93	4.5 %	85	14.5 %	<0.001		
Pregnancy (n, %)	86	4.1 %	13	2.2 %	0.02		
Obesity (n, %)	681	32.8 %	188	32.0 %	0.7		
Diabetes mellitus (n, %)	327	15.8 %	106	18.0 %	0.2		
HIV (n, %)	37	1.8 %	27	4.6 %	<0.001		
Immunodeficiency (n, %)	149	7.2 %	134	22.8 %	<0.001	3.5 (2.6–4.9)	<0.001
Early oseltamivir treatment (n, %)	1254	60 %	352	59.4 %	0.8		
Appropriate antibiotic therapy (n, %)	259	85.2 %	122	83.0 %	0.5		
Corticosteroids (n, %)	408	19.5 %	121	20.4 %	0.6		
Acute kidney injury (n, %)	348	19.0 %	280	49.6 %	<0.001		
Continuous renal replacement therapy (n, %)	93	4.9 %	161	28.4 %	<0.001	4.0 (2.9–5.6)	<0.001
Invasive mechanical ventilation (n, %)	1108	53.0 %	541	91.2 %	<0.001	4.9 (3.5–6.9)	<0.001
Septic shock (n, %)	921	44.0 %	475	80.1 %	<0.001		
Bacterial co-infection (n, %)	304	14.5 %	147	24.8 %	<0.001	1.4 (1.1–1.8)	0.02

Variables that were evaluated for inclusion in the multivariate logistic regression model: age, gender, APACHE II score, asthma, congestive heart failure, chronic kidney disease, haematological patients, pregnancy, HIV, immunodeficiency, appropriate antibiotic, acute kidney injury, continuous renal replacement therapy, invasive mechanical ventilation, septic shock and presence of co-infection

APACHE Acute Physiology and Chronic Health Evaluation, *HIV* human immunodeficiency virus, *OR* odds ratio

our study the rate of empirical administration of antiviral agents was high (70 %), and almost all patients received antiviral treatment at the time the PCR became positive (96.6 %). There were no differences in the antiviral treatment given to patients presenting with or without co-infection that could explain why co-infection patients experienced a worse outcome. Interestingly, patients with co-infection experienced a longer delay in the diagnosis of influenza and admission to ICU; however, the number of days from symptom onset to antiviral treatment was not different between those with and without co-infection. These patients may have been diagnosed initially as having community-acquired pneumonia, pending the result of a positive PCR test result for influenza. In spite of this, no difference in the number of days between admission to hospital and antiviral administration was observed between the patients with and without co-infection (5.1 days in both groups). A very surprising finding was the lack of association between appropriate antibiotic use and outcome. Appropriate antibiotic administration has been repeatedly associated with better outcomes in patients with community-acquired pneumonia [25]. Whilst co-infection was associated with worse outcome, and conversely appropriate antibiotic use did not result in better survival, we speculate that there is an unknown and complex host–pathogen interaction that can explain this finding. Another point is that among all the comorbidities, only severe immunosuppression was associated with worse outcome, supporting the major role of the immune system in the physiopathology of influenza in critically ill patients.

This study describes the clinical characteristics and outcome of the largest series of patients with confirmed RT-PCR influenza to date. The main strength of the study is its prospectively collected, consecutive design that has systematically followed up patients in 148 ICUs throughout Spain. The systematic inclusion of patients in this study and the detailed clinical characteristics recorded have allowed the Spanish healthcare system to determine and monitor patients' characteristics, mortality rates and rate of co-infection. No other European multicentre study with prospective collection of data from critically

ill patients over a period of several years has been published. We recognize that the epidemiology elsewhere may differ; however, it seems likely that in other countries around the globe have a larger population of vulnerable patients (immunosuppressed persons and the elderly) and a higher rate of co-infection than in Spain. Recent studies conducted to identify the epidemiology of pathogens in patients with either community-acquired pneumonia or healthcare-associated pneumonia showed low rates of resistant pathogens in Europe [25]. The changes in the epidemiology of co-infection demonstrated in our study therefore need to be confirmed in other countries, especially in those with higher rates of resistant pathogens.

Several limitations in the design of our study need to be acknowledged. Firstly, in 7.4 % of the patients the outcome was missing. The observational nature of the study does not allow estimation of the cause-and-effect relationship between the risk factors and outcome, as additional confounding factors may not have been identified (risk factors for healthcare-associated pneumonia, timing of antibiotic administration etc.). Of note, four episodes of *Staphylococcus hominis* bacteraemia might be related intravascular catheter-related infections, and diagnosis of aspergillosis was done after ICU admission in all cases but the exact date of a positive result was not captured. Co-infection diagnosis was not standardized and was based mainly on tracheal aspirate obtained immediately after intubation rather than other invasive diagnostic techniques. During the influenza periods, bronchoalveolar lavage was not systematically performed because of the high risk of generating aerosols. Bronchoscopic lavage, protected specimen brushing and transbronchial or transthoracic lung biopsies have potential risks in severely hypoxaemic intubated patients and are uncommon for standard management of patients with severe community-acquired pneumonia [26] [11]. Data on antibiotics timing and patients receiving antibiotics before bacterial sampling were not recorded as per the design of the study.

Secondly, as mentioned above, this study was restricted to Spanish ICUs, so the findings may not be applicable to non-ICU settings or to other countries. Obviously, ICU admission and criteria for endotracheal intubation were not standardized. In addition, 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 [27]. However, significant promotion of awareness over the years by regulatory agencies such as the Centers for Disease Control and Prevention and the World Health Organization has helped physicians to treat patients promptly and adequately [28].

Conclusion

In summary, our results reveal that co-infection is diagnosed in one out of every six critically ill patients admitted to the ICU with severe influenza virus infection, with an increasing tendency over recent epidemics. Co-infection in influenza is an independent risk factor associated with higher ICU mortality because almost all patients (with or without co-infection) received antimicrobial therapy. Surprisingly, the use of appropriate antibiotic therapy was not associated with an improved outcome. The virulence of influenza and complex host–pathogen interactions in patients with co-infection deserve further attention in both epidemiological and translational research. This study is the first to show that there is a trend to more co-infection, which is independently associated with worse outcome.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-016-4578-y) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
All of the authors declare that no conflict of interest exists.

Role of funding source
The study funder (Spanish Society of Critical Care—SEMICYUC) had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (IML) had full access to all the data in the study and final responsibility for the decision to submit for publication.

Ethics committee approval
The institutional review board of Joan XXIII University Hospital approved the original study (IRBref#11809).

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