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Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection

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Abstract *Introduction:* Early use of corticosteroids in patients affected by pandemic (H1N1)v influenza A infection, although relatively common, remains controversial. *Methods:* Prospective, observational, multicenter study from 23 June 2009 through 11 February 2010, reported in the European Society of Intensive Care Medicine (ESICM) H1N1 registry. *Results:* Two hundred twenty patients admitted to an intensive care unit (ICU) with completed outcome data were analyzed. Invasive mechanical ventilation was used in 155 (70.5%). Sixty-seven (30.5%) of the patients died in ICU and 75 (34.1%) whilst in hospital. One hundred twenty-six (57.3%) patients received corticosteroid therapy on admission to ICU. Patients who received corticosteroids were significantly older and were more likely to have coexisting asthma, chronic obstructive pulmonary disease (COPD), and chronic steroid use. These patients receiving corticosteroids had increased likelihood of developing hospital-acquired pneumonia (HAP) [26.2% versus 13.8%, $p < 0.05$; odds ratio (OR) 2.2, confidence interval (CI) 1.1–4.5]. Patients who received corticosteroids had significantly higher ICU mortality than patients who did not (46.0% versus 18.1%, $p < 0.01$; OR 3.8, CI 2.1–7.2). Cox regression analysis adjusted for severity and potential confounding factors identified that early use of corticosteroids was not significantly

associated with mortality [hazard ratio (HR) 1.3, 95% CI 0.7–2.4, $p = 0.4$] but was still associated with an increased rate of HAP (OR 2.2, 95% CI 1.0–4.8, $p < 0.05$). When only patients developing acute respiratory distress syndrome (ARDS) were analyzed, similar results were observed.

Conclusions: Early use of corticosteroids in patients affected by pandemic (H1N1)v influenza A infection did not result in better outcomes and was associated with increased risk of superinfections.

Introduction

Pandemic (H1N1)v influenza A infection was first described in Mexico in April 2009, and on 11 June 2009 the World Health Organization (WHO) declared the new flu as the first pandemia of the 21 century, by which time mortality rates were being reported to be as high as 38% [1] with similar rates being reported in all continents: Spain (25%) [1], Canada (17.3%) [2], Australia and New Zealand (14.3%) [3], and Argentina (46%) [4].

The efficacy of systemic corticosteroids has been extensively studied in acute respiratory distress syndrome (ARDS). While they clearly have a role in situations where ARDS has been precipitated by a corticosteroid-responsive process (e.g., acute eosinophilic pneumonia), the value of corticosteroid therapy in most other cases remains uncertain [5]. In the 1970s and early 1980s, empirical corticosteroids were widely used to treat ARDS; however, corticosteroid therapy in this setting subsequently became less frequent after several studies found that they had no benefit and may actually cause harm [6, 7]. Since then, several meta-analyses and reviews have been published offering conflicting perspectives regarding corticosteroid treatment for ARDS [8–11].

The most common pulmonary presentation of patients affected by pandemic (H1N1)v influenza A infection is rapidly progressive viral pneumonia with bilateral alveolar infiltrates on chest radiography, and ARDS [12]. The presentation of ARDS with severe refractory hypoxemia has been particularly common in patients with this disease process and might be linked to an abnormal immune response [13]. Several published reports of pandemic (H1N1)v influenza A infection [2, 14] have reported use of empirical corticosteroid therapy in more than half of these patients, both as primary therapy and as rescue therapy for patients with severe ARDS. Recent guidelines for management of human infection with pandemic (H1N1)v influenza A infection recommend that corticosteroid therapy should not be used routinely, although low doses may be considered for patients in septic shock who require vasopressors and have suspected adrenal insufficiency [15, 16]. Data supporting this guidance, however, remain scarce and controversial [17]. A single prospective interventional study with only 13 patients by Quispe-Laime et al. [18] demonstrated that a prolonged low to moderate dose of corticosteroid treatment was associated with significant improvement in lung injury and multiple organ dysfunction scores and reduced hospital mortality rate.

The main objective of this study is therefore to assess the effect on survival of early corticosteroid therapy compared with those who did not receive corticosteroids or received them subsequently as rescue therapy, in a cohort of patients hospitalized with severe presentation of pandemic (H1N1)v influenza A infection in the ICU.

Materials and methods

Data for this study were obtained from a voluntary registry instituted by the European Society of Intensive Care Medicine (ESICM). The registry contains data from patients admitted to the ICU with confirmed, probable or suspected pandemic (H1N1)v influenza A infection. All reports notified before 11 February 2010 were eligible for inclusion. Ethical approval was sought and obtained where necessary prior to any patients being entered into the registry. All patients enrolled were recorded into the registry in an anonymous format. The need for informed consent was waived due to the observational nature of the study and the fact that this activity was an emergency public health response.

The inclusion criteria for this study consisted of: fever (>38°C); acute illness; respiratory symptoms consistent with cough, sore throat, myalgia or influenza-like illness; and acute respiratory failure requiring ICU admission with confirmed, probable or suspected pandemic (H1N1)v influenza A infection, according to case definitions developed by the World Health Organization (WHO) [19, 20]. A "confirmed case" was defined as an acute respiratory illness with laboratory-confirmed pandemic (H1N1)v influenza A virus infection with real-time reverse-transcription polymerase chain reaction (RT-PCR) or viral culture [20]. All tests and procedures were ordered by attending physicians.

The definitions of community-acquired pneumonia and hospital-acquired pneumonia were based on 2007 American Thoracic Society and Infectious Disease Society of America guidelines [21]. Primary viral pneumonia

was defined in patients presenting during the acute phase of influenza virus illness with ARDS and unequivocal alveolar opacification involving two or more lobes with negative respiratory and blood bacterial cultures. Secondary bacterial pneumonia was considered in patients with confirmation of influenza virus infection who showed recurrence of fever, increase in cough, and production of purulent sputum with in addition positive respiratory pathogens or blood cultures [22]. Microbiological confirmation of HAP was based on standardized procedures at each investigator site. Acute renal failure was defined as need for renal replacement therapy following the International Consensus Conference [23]. Obese patients were defined as those with body mass index (BMI) over 30 kg/m^2 [24]. ICU admission criteria and treatment decisions for all patients, including determination of need for intubation and type of antibiotic and antiviral therapy administered, were made by the attending physician. The following information was also recorded: demographic data, comorbidities, time of illness onset and hospital admission, time to first dose of antiviral therapy, microbiologic findings, and chest radiographic findings at ICU admission. Intubation and mechanical ventilation requirements, adverse events during ICU stay (e.g., need for vasopressor drugs, or renal replacement techniques), and laboratory findings at ICU admission were also recorded. To determine illness severity, the Simplified Acute Physiology Score (SAPS3) [25, 26] and the Acute Physiology and Chronic Health Evaluation (APACHE) II score [27] were determined in all patients within 24 h of ICU admission. In addition, organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) scoring system [28].

Systemic corticosteroid use was considered when dosages equivalent to >24 mg/day methylprednisone or >30 mg/day prednisone were given at ICU admission. Patients who received corticosteroid therapy on ICU admission were compared with those who did not receive corticosteroid therapy or who received them subsequently as rescue therapy for unfavorable clinical progression.

Statistical analysis

Discrete variables are described as counts (%) and continuous variables as mean with standard deviation (SD) or median with 25th to 75th interquartile range (IQR), as appropriate. Unless otherwise stated, all statistical tests were two sided and $p < 0.05$ was considered significant. Differences in categorical variables were calculated using the two-sided likelihood ratio, chi-square test or Fisher's exact test, and the Mann–Whitney U test or Kruskal–Wallis test was used for continuous variables, when appropriate. Cox proportional-hazards regression analysis was used to assess the impact of independent variables on ICU mortality across time. Variables significantly associated with mortality on univariate analysis were entered into the model. To avoid spurious associations, variables entered into the regression models were those with a relationship on univariate analysis ($p \leq 0.05$) or a plausible relationship with the dependent variable. Results are presented as hazard ratio (HR) and 95% confidence interval (CI). Potential explanatory variables were checked for collinearity prior to inclusion in the regression models using tolerance and variance inflation factor. Data analysis was performed using SPSS 13.0 (SPSS, Chicago, IL, USA) for Windows.

Results

Two hundred twenty patients with completed outcomes from the ESICM H1N1 registry were analyzed in this study. All patients had suspected, probable or confirmed pandemic (H1N1)v influenza A infection and were being cared for in an ICU. One hundred ninety-four were confirmed (88.2%), 2 were probable (0.9%), and 24 patients were suspected (10.9%) for pandemic (H1N1)v influenza A virus. Of these, 113 patients were male (51.4%) with median age of 43 (IQR 32–55) years, and 188 (85.5%) were under 60 years of age. The mean SAPS3 score was 53.0 ± 16.2 and the mean SOFA score was 8.2 ± 4.2 on admission. Mechanical ventilation was used in 171 (77.7%) of the patients, 155 (70.5%) with invasive modes and 65 (29.5%) noninvasively; 49 (75.3%) of the patients having noninvasive modes of ventilation subsequently required invasive ventilation. All patients received antiviral therapy. Oseltamivir administration delay after illness onset did not differ between early corticosteroid uses. ARDS was present in 74.3% patients. Comorbidities were present in 107 (48.6%) patients. Obesity ($n = 67$, 30.5%), asthma ($n = 24$, 10.9%), and chronic obstructive pulmonary disease (COPD, $n = 23$ 10.5%) were the main comorbidities reported.

One hundred twenty-six (57.3%) patients received early corticosteroid therapy at ICU admission. Patients surviving the ICU stay and receiving corticosteroids early on ICU admission had mean duration of corticosteroid therapy of 10.3 ± 11.7 days. ICU length of stay in survivors did not differ in patients who received early corticosteroids compared with those who did not (12.9 ± 14.0 versus 10.8 ± 9.8 days, $p = 0.29$). Patients who received early corticosteroid therapy were significantly older (46.2 ± 14.9 versus 39.4 ± 17.1 years, $p < 0.001$) and had asthma [19 (15.1%) versus 5 (5.3%), $p < 0.001$], COPD [19 (15.1%) versus 4 (4.3%), $p < 0.01$], and chronic steroid use [24 (19%) versus 4 (4.3%), $p < 0.01$] more frequently than patients who did not. Patients who received early corticosteroid therapy were sicker than those who did not receive them according to SAPS3 data (55.9 ± 16.8 versus 49.0 ± 14.5, $p = 0.001$). No differences were found

between patients who were or were not treated with early corticosteroid therapy regarding prevalence of ARDS (70.4% versus 77.3%, p 0.3). Mechanical ventilation was based on lung protective strategies. For the entire cohort, tidal volume was 5.7 (IQR 4.7–6.5) ml/kg ideal body weight (IBW). We did not find any differences between tidal volume in patients who received early corticosteroid therapy compared with those who did not [5.6 (IQR 4.7–6.3) versus 5.7 (IQR 4.8–7.5) ml/kg IBW, $p = 0.2$]. Additional demographic data and clinical characteristics of patients with pandemic (H1N1)v influenza A with and without early corticosteroid therapy are presented in Table 1.

Hospital-acquired pneumonia was clinically suspected in 79 patients (35.9%), with microbiological documentation in 46 patients (20.9%) patients. Patients who received early corticosteroid therapy had HAP more frequently than patients who did not [26.2% versus 13.8%, $p < 0.05$; odds ratio (OR) 2.2, CI 1.1–4.5]. Since the severity of illness of patients who received early corticosteroid therapy was higher, multivariate regression analysis adjusting for severity was performed and confirmed the higher incidence of HAP in patients who received early corticosteroid therapy [OR = 2.2 95%, confidence interval (CI) 1.0–4.8; $p < 0.05$]. *Pseudomonas aeruginosa* ($n = 13$, 28.3%) was identified as the most prevalent pathogen, followed by *Acinetobacter baumannii* ($n = 7$, 15.2%) and *Streptococcus pneumoniae* ($n = 5$, 10.9%) (Table 2).

In total, 67 patients died on the ICU (30.5%) and 75 (34.1%) whilst in hospital. Nonsurvivors presented with significantly higher SAPS3 score at admission (61.9 ± 18.5 versus 47.7 ± 11.9, $p < 0.01$) and higher

SOFA score (10.1 ± 4.2 versus 6.7 ± 3.7, $p < 0.01$) when compared with survivors. The characteristics of the patients who died are shown in Table 3. Patients who received early corticosteroid therapy on ICU admission had significantly higher ICU mortality than those who did not (46.0% versus 18.1%; OR 3.8, CI 2.1–7.2; $p < 0.01$). This association with increased mortality was not present when mortality data were adjusted for increased severity of illness (SAPS3) and other known confounding variables (age, COPD, asthma, and chronic steroid use) [hazard ratio (HR) 1.3 95%, CI 0.7–2.4; $p = 0.4$] (Fig. 1). Similar findings were found when repeating the analysis for only the cohort of patients who presented with ARDS (HR 1.1, 95% CI 0.5–2.3; $p = 0.7$).

Discussion

This analysis of a large, cohort, prospective, multicenter research study suggests that prompt use of corticosteroid therapy on ICU admission does not result in a reduction of mortality for critically ill patients admitted with pandemic (H1N1)v influenza A infection. Furthermore, there is also not a beneficial effect of early corticosteroid therapy when given to the more severe end of the spectrum of patients requiring invasive mechanical ventilation for ARDS. Another important finding of this study was that patients receiving early corticosteroid therapy had increased likelihood of developing superadded bacterial infection.

Endogenous glucocorticoids as end-effectors play a role in inhibiting inflammation [29] but are not always effective in suppressing the "cytokine storm" driven by

Table 1 Comparison of demographic and clinical characteristics among patients with pandemic (H1N1)v influenza A infection with or without early corticosteroid therapy

Risk factor	Overall population ($n = 220$)	Early corticosteroid therapy ($n = 126$)	No early corticosteroid therapy ($n = 94$)	p-Value
Male, n (%)	113 (51.4%)	68 (54.0%)	45 (47.9%)	0.4
Age, mean (SD), years	43.26 (16.2)	46.17 (14.9)	39.37 (17.11)	<0.001
Obesity, n (%)	67 (30.5%)	44 (34.9%)	23 (24.5%)	0.1
Diabetes, n (%)	33 (15.0%)	19 (15.1%)	14 (14.9%)	0.99
Chronic renal failure, n (%)	15 (6.8%)	9 (7.1%)	6 (6.5%)	0.99
Valvular disease, n (%)	6 (2.7%)	3 (2.4%)	3 (3.2%)	0.7
Ischemic cardiomyopathy, n (%)	13 (5.9%)	8 (6.3%)	5 (5.3%)	0.99
Asthma, n (%)	24 (10.9%)	19 (15.1%)	5 (5.3%)	<0.001
Arrhythmia, n (%)	10 (4.6%)	8 (6.4%)	2 (2.1%)	0.2
COPD, n (%)	23 (10.5%)	19 (15.1%)	4 (4.3%)	<0.01
Cerebrovascular disease, n (%)	6 (2.7%)	4 (3.2%)	2 (2.1%)	0.99
Hematological malignancy, n (%)	15 (6.8%)	9 (7.1%)	6 (6.4%)	0.99
Peripheral vascular disease, n (%)	4 (1.8%)	3 (2.4%)	1 (1.1%)	0.6
Cirrhosis, n (%)	7 (3.2%)	3 (2.4%)	4 (4.3%)	0.4
Seizure, n (%)	10 (4.6%)	4 (3.2%)	6 (6.4%)	0.3
Chronic steroid use, n (%)	28 (12.7%)	24 (19.0%)	4 (4.3%)	<0.001

COPD chronic obstructive pulmonary disease

Table 2 Prevalence of pathogens isolated in patients with HAP according to use of early corticosteroid therapy

Risk factor	Overall population (n = 46)	Early corticosteroid therapy (n = 33)	No early corticosteroid therapy (n = 13)
P. aeruginosa	13 (28.3%)	12 (92.3%)	1 (7.7%)
A. baumannii	7 (15.2%)	5 (71.4%)	2 (28.6%)
S. pneumoniae	5 (10.9%)	4 (80.0%)	1 (20.0%)
S. aureus[a]	5 (10.9%)	2 (25.0%)	3 (75.0%)
Aspergillus spp.	4 (8.7%)	3 (75.0%)	1 (25.0%)
K. pneumoniae	3 (6.5%)	2 (66.7%)	1 (33.3%)
E. coli	2 (4.3%)	2 (100%)	0
H. influenza	2 (4.3%)	2 (100%)	0
E. cloacae	2 (4.3%)	1 (50%)	1 (50%)
E. aerogenes	1 (2.2%)	0	1 (100%)
S. marcescens	1 (2.2%)	0	1 (100%)
S. maltophila	1 (2.2%)	0	1 (100%)

[a] Including one episode of oxacillin-resistant S. aureus

Table 3 Comparison of demographic and clinical characteristics among patients with pandemic (H1N1)v influenza A infection who died versus survived

| Risk factor	Alive (n = 145)	Death (n = 75)	p-Value
Male, n (%)	69 (47.6%)	44 (58.7%)	0.1
Age, mean (SD), years	41.7 (15.3)	46.1 (17.4)	0.05
Obesity, n (%)	43 (29.7%)	24 (32.0%)	0.7
Diabetes, n (%)	22 (15.2%)	11 (14.7%)	0.9
Chronic renal failure, n (%)	8 (5.6%)	7 (9.3%)	0.3
Valvular disease, n (%)	3 (2.1%)	3 (4.0%)	0.4
Ischemic cardiomyopathy, n (%)	8 (5.5%)	5 (6.7%)	0.7
Asthma, n (%)	19 (13.1%)	5 (6.7%)	0.2
Arrhythmia, n (%)	6 (8.0%)	2 (2.7%)	0.2
COPD, n (%)	13 (9.0%)	10 (13.3%)	0.3
Cerebrovascular disease, n (%)	3 (2.1%)	3 (4.0%)	0.4
Hematological malignancy, n (%)	7 (4.8%)	8 (10.7%)	0.1
Peripheral vascular disease, n (%)	2 (1.4%)	2 (2.7%)	0.6
Cirrhosis, n (%)	2 (1.4%)	5 (6.7%)	<0.05
Seizure, n (%)	8 (5.5%)	2 (2.7%)	0.5
MV, n (%)	83 (57.2%)	72 (96.0%)	<0.001
Chronic steroid use, n (%)	16 (11.0)	12 (16.0)	0.3

COPD chronic obstructive pulmonary disease, MV mechanical ventilation

systemic inflammation, even though cortisol levels have been correlated with grades of illness severity and mortality [30]. With the concept of critical-illness-related corticosteroid insufficiency (CIRCI) [31] and the results of clinical trials showing respiratory immune and hemodynamic benefits, corticosteroid therapy has re-emerged as a promising adjunct for treatment of severe sepsis.

Severe bacterial pneumonia is associated with relative corticosteroid insufficiency as well as a plethora of other pulmonary and systemic effects [32]. This inflammatory cascade can be partially blocked by administration of systemic corticosteroid therapy [33]. The more severe the presentation, the worse the inflammatory crisis, therefore previous authors have suggested that steroid therapy should be more effective in more severely ill patients [34–36]. This is not what was shown in the present study. Recent guidelines for management of community-acquired pneumonia suggest the benefit of systemic corticosteroid therapy for patients with severe presentation [37]. This has been shown in one small randomized controlled study with hydrocortisone treatment, terminated prematurely due to 0% mortality in the intervention arm and a significant reduction in length of hospital stay [38]. More recently, Snijders et al. [39] conducted a randomized controlled trial in 213 hospitalized patients with CAP. These patients were randomized to receive either 40 mg prednisolone for 7 days or placebo added to antibiotic therapy. This study did not show any differences in clinical outcomes in either the overall population or those with severe pneumonia. Additionally, late clinical failure (>72 h after hospital admission) was more common in the prednisolone group than in the placebo group.

Data supporting use of corticosteroid therapy in patients affected by primary viral pneumonia are limited
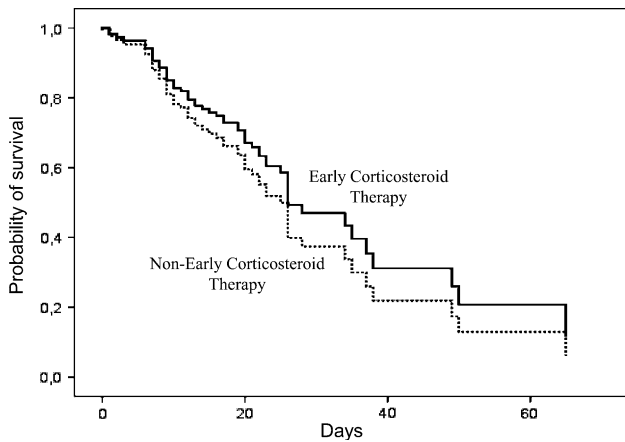
Fig. 1 Survival graph for patients with severe pandemic (H1N1)v influenza A infection with or without early corticosteroid therapy on ICU admission (censored at 60 days)

at the present time, with some reports extrapolating from the 2002–2003 severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak [40–42] to the current pandemic. The innate antiviral host response is based on early elevated expression of CXCL10, CCL2, and CCL4 in SARS-CoV and human respiratory syncytial virus (hRSV)-infected patients [43–45]. Use of corticosteroid therapy is a double-edged sword. Li et al. [46] reported that high doses of corticosteroids decrease immunity by reducing CD4, CD8, and CD3 levels in patients with SARS and result in an increase in secondary infections; moreover, Tsang et al. [47] found an increase in 30-day mortality in the same subset of patients. Nevertheless, the exact mechanism of corticosteroid therapy needs to be further elucidated due to the fact that there is no evidence of benefit in SARS in the early phase when SARS-CoV replication is still ongoing. Lee et al. [48] found that SARS-CoV load was significantly higher in the second and third week of illness in patients who received initial corticosteroid therapy.

Recent results from the CORTICUS study [49] do not support routine use of corticosteroid therapy in patients with septic shock, because they showed only a beneficial effect of stress doses of corticosteroids in decreasing time to shock reversal [50] but not on 28-day mortality, an effect at least in part explained by an increased risk of superinfection. Use of corticosteroid therapy also exerts a decisive influence on the immune function of macrophages and granulocytes, the main cell host defenses against bacteria [51]. In the present study there was significant incidence of nosocomial infections that resulted in twofold higher incidence of hospital-acquired pneumonia in patients who received corticosteroid therapy. Incidence of HAP due to *Pseudomonas aeruginosa* was 92.3% and due to *Acinetobacter baumannii* was 71.4% in the corticosteroid group. Additionally, one of the most intriguing observations was that four patients developed ventilator-associated pneumonia (VAP) due to *Aspergillus* spp., three of whom were receiving corticosteroid therapy.

The present study has several potential limitations that should be addressed. First is that only patients treated with early corticosteroid therapy on ICU admission were considered in the treatment group. The control group comprised patients who did not receive early corticosteroid therapy and those who received them subsequently as rescue therapy. Use of corticosteroid therapy after ICU admission was not considered in the treatment group, since this subgroup of patients would be considered as receiving rescue therapy due to unfavorable clinical progression. No data were available to subanalyze the role of rescue therapy; nevertheless, the multivariate analysis was adjusted for severity as well as other confounding factors to avoid a potential bias that might invalidate our final conclusions. Secondly, this is an observational, noninterventional study, in which the participating ICUs from 23 countries in the world were self-selected. Prescription of corticosteroids was chosen in accordance with local protocols. To correct for differences in different corticosteroid therapies, treatment class was homogenized so that systemic corticosteroid use was considered when dosages equivalent to >24 mg/day methylprednisone or >30 mg/day prednisone were given acutely on ICU admission, as reported in previous studies [52]. Thirdly, in spite of the fact that microbiological confirmation based on current Infectious Disease Society of America (IDSA)/ American Thoracic Society (ATS) guidelines [53] would be preferable, bronchoscopic procedures were not performed routinely because of severe hypoxemia complicating ARDS (H1N1)v episode and safety concerns regarding generation of aerosols. Finally, dosing of oseltamivir was left to the discretion of the attending physician and was not standardized. It is crucial to note that underdosing is a common problem in patients with severe sepsis and mechanical ventilation who have a high volume of distribution and low enteral absorption [54]. Ariano et al. [55] recently reported that dosage of 75 mg twice-daily achieved plasma levels that were comparable to those in ambulatory patients and were far in excess of concentrations required to maximally inhibit neuraminidase activity of the virus.

There is little definitive evidence of either benefit or harm from early corticosteroid use as routine adjunctive treatment in patients affected by pandemic (H1N1)v influenza A infection. Nevertheless, the results drawn from this study show that such early use did not result in better outcomes and may be associated with increased risk of superadded infections.

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