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MINIREVIEWS

Corticosteroids for severe influenza pneumonia: A critical appraisal

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Abstract

Influenza pneumonia is associated with high number of severe cases requiring hospital and intensive care unit (ICU) admissions with high mortality. Systemic steroids are proposed as a valid therapeutic option even though its effects are still controversial. Heterogeneity of published data regarding study design, population demographics, severity of illness, dosing, type and timing of corticosteroids administered constitute an important limitation for drawing robust conclusions. However, it is reasonable to admit that, as it was not found any advantage of corticosteroid therapy in so diverse conditions, such beneficial effects do not exist at all. Its administration is likely to increase overall mortality and such trend is consistent regardless of the quality as well as the sample size of studies. Moreover it was shown that corticosteroids might be associated with higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay. Finally, it is reasonable to conclude that corticosteroids failed to demonstrate any beneficial effects in the treatment of patients with severe influenza infection. Thus its current use in severe influenza pneumonia should be restricted to very selected cases and in the setting of clinical trials.

Key words: Influenza; Mechanical ventilation; Pneumonia; Corticosteroids; Respiratory failure

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Core tip: This review article presents a critical appraisal

to the use of corticosteroids in severe influenza infections covering the most relevant clinical studies, underlying mechanisms (pathophysiologic and pharmacologic aspects) and providing a scenario to help clinicians at bedside facing this challenging situation.

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INTRODUCTION

According to the World Health Organization, lower respiratory tract infections account for approximately 7% of deaths per year worldwide and viruses are a common cause of community-acquired pneumonia[1]. Among this wide group of species, influenza virus are of utmost importance and numerous interventions have been proposed for its management[2], especially after pandemic H1N1 influenza virus outbreak, which was associated with high number of severe cases requiring hospital and intensive care unit (ICU) admissions and resulted in ICU mortality rates ranging from 14% to 46%[3].

Systemic steroids are proposed as a valid therapeutic option due to their potential role in controlling host inflammatory response, inhibiting cytokine production and restoring the inappropriately low endogenous cortisol levels, compensating critical illness-related corticosteroid insufficiency[4]. Although widely used in H1N1 pandemics, the effect of corticosteroids is still controversial. The purpose of this review is to provide an overview of published data about steroid use and outcomes in severe influenza infection.

Influenza infection

Influenza viruses are enveloped negative-sense RNA viruses with segmented genomes that belong to the family *Orthomyoviridae*[5]. There are three antigenically distinct subtypes, A, B and C, which circulate among humans worldwide[6].

Three influenza pandemics occurred in the 20th century[5,7]: 1918 (Spanish influenza), 1957 (Asian influenza) and 1968 (Hong Kong influenza). Different antigenic subtypes of influenza A caused them, each resulting in more than a million deaths. In 2009, a pandemic H1N1 virus developed by reassortment among several influenza A strains. Over 18000 deaths were laboratory confirmed cases but experts agree that more than 250000 deaths may have resulted from H1N1 infection[8].

The 2009 H1N1 influenza pandemic originated a surge of research investigating the mechanisms of lung injury that develop in severe cases of influenza infection, complementing the work started six years before, after the SARS (Severe Acute Respiratory Syndrome) global outbreak.

Seasonal influenza is an acute respiratory disease that presents with sudden onset of high fevers, upper respiratory tract symptoms, chills, myalgia and gastrointestinal tract symptoms. Infection rarely induces symptoms of lower respiratory tract infections or severe lung injury. Pandemic H1N1 infected patients presented with fever, cough and sore throat and the most severe case rapidly developed bilateral pneumonia, severe ARDS, multiple organ failure and death[9,10]. It affected young individuals disproportionately and several epidemiological studies suggested that pregnant women and obese patients were more susceptible to severe infection[5].

Although molecular mechanisms underpinning these associations are not completely understood, it is known that adipocytes and macrophages from obese patients release higher quantities of interleukin (IL)-6 and tumor necrosis factor (TNF)-α when compared to non-obese patients[11]. Hypercytokinemia and a proinflammatory state are related to disease severity in influenza infections. Furthermore, the proinflammatory properties of lectin and anti-inflammatory properties of adiponectin may increase the risk of developing hypoxemic respiratory failure[11]. Biomarkers of endothelial injury (surfactant protein D and von Willebrand factor) were found to be elevated in obese patients with hypoxemic respiratory failure[12]. The likelihood of a combined influenza induced epithelial and endothelial injury is corroborated by pathology reports of pandemic H1N1 patients' lung specimens which showed extensive diffuse alveolar damage, variable degrees of pulmonary hemorrhage (with evidence of perivasculitis and microthrombi) and necrotizing bronchiolitis[13]. Persistence of viral shedding has recently been associated with poorer outcome and longer hospital stay both as a predisposing factor and as a complication of influenza infection[14].

Corticosteroid pharmacology

Corticosteroids are cyclic organic compounds physiologically secreted by zona fasciculata cells of the adrenal cortex. Under physiological circumstances, its synthesis and secretion are tightly regulated by the central nervous system, through the pituitary release of corticotropin (ACTH), which is very sensitive to negative feedback by the circulating cortisol and exogenous (synthetic) glucocorticoids[15]. Cortisol, the main human corticosteroid, has a half-life of 60 to 90 min which can be significantly increased with large steroid loads. The volume of distribution (Vd) also increases with higher steroid doses and both parameters are agent-specific[16]. Corticosteroids are metabolized through complexly regulated enzymatic transformations in the liver [through A-ring reductases (5β-reductase and 5α-reductase)] and kidney [through 11-β hydroxysteroid dehydrogenase type 2 (11β-HSD2)][17,18] that diminish their physiologic activity and increase water solubility to enhance their

urinary excretion[15]. Most of the known effects of the corticosteroids are mediated by nuclear receptors.

Corticosteroids in critical illness

Interest in the role of corticosteroids in the pathophysiology of critical illness has existed since the early decades of the 20th century[19] Every acute physical stress or noxious stimuli results in a coordinated systemic response classically referred to as stress response or general adaption syndrome. Among the physiological responses to stress, hypercortisolemia is proportionate to the severity of illness[20]. Such response has traditionally been attributed to activation of the hypothalamic-pituitary-adrenal (HPA) axis[21] with increased secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone which stimulates the production of ACTH by the anterior pituitary gland, causing a sustained increase in cortisol secretion. This increased corticotropin-driven cortisol production originates multiple effects (metabolic, cardiovascular and immune) aimed at restoring homeostasis during stress[17].

Since the late 90's a paradoxical dissociation between cortisol and corticotropin (slightly elevated or even normal to low levels of corticotropin with permanently high cortisol levels) has been observed during critical illness[22,23]. As a consequence, explanations for hypercortisolemia other than increased cortisol production due to HPA axis activation have been pursued. Proinflammatory cytokines (TNF-α and IL-6), neuropeptides and cathecolamines correlate positively with cortisol production and are independent of HPA axis[24]. The possibility of an increased sensitivity to corticotropin was formulated but considered unlikely because cortisol plasmatic levels were not consistently elevated after exogenous corticotropin stimulation[17,25]. The reduction of cortisol metabolism during critical illness emerged as an alternative or additional mechanism with recent data showing suppression of activity of cortisol metabolizing enzymes in critical care patients. Boonen *et al*[18] found evidence of impaired 11β-HSD2 function and reduction of A-ring reductases activity that may be mediated by bile acids, known competitive inhibitors and transcriptional suppressors of cortisol-metabolizing enzymes.

The possibility that reduced cortisol breakdown is a main contributor to hypercortisolemia during critical illness may changes our conceptual understanding of the stress response. It could mean that low cortisol metabolism with hypercortisolemia would have induced a negative feedback on the HPA-axis resulting in lower corticotropin levels and adrenocortical atrophy. Such effect implies the downregulation or functional inactivation of corticotropin receptors on adrenocortical cells, which would explain the low cortisol response to corticotropin stimulation. Moreover, reduced cortisol inactivation may also potentiate cortisol activity within the vital tissues that express inactivating enzymes[18], what suggests that corticosteroids stress doses in critically ill patients are at least three times too high. These facts imply that the concept of critical illness associated adrenal failure may not be real and question the pathophysiological principles of corticosteroids stress doses in acute injuries.

Observational studies

According to observational data, approximately one third of 2009 H1N1 pandemia cases reported were treated with corticosteroids[26] both as a primary therapy or as a rescue therapy for patients with severe ARDS[27,28]. Despite this, a standard steroid and dose regimen are not well established and its efficacy and safety are not entirely clear.

In general, therapy with steroids in severe infections has shown to be beneficial in a pair of clinical situations: bacterial meningitis in immunocompetent hosts[29] and Pneumocystis jiroveci pneumonia in HIV patients[30]. In other conditions, like severe CAP and ARDS (due to pneumonia or not), no positive impact on mortality has been shown, still being an unresolved matter that deserves further investigation[4].

A common pulmonary presentation of patients affected by pandemic (H1N1) influenza A infection is rapidly progressive pneumonia with bilateral alveolar infiltrates on chest radiography and ARDS, that might be linked to an abnormal immune response[31]. The role of steroids as adjunctive therapy in influenza is very attractive theoretical approach to try to modulate hypercytokinemia associated with the most severe presentation[4]. However, a balance must occur between this phenomenon and the possibility of prolonged viral replication, resulting in more direct cytopathic effect on the infected lungs[32].

The main observational studies on corticosteroid treatment in influenza infected patients are listed in Table 1. All but one[33] evaluate steroids use in H1N1 infections. Xi *et al*[34] retrospectively evaluated data from 155 adults with confirmed H1N1 infection in China, one-third (33.5%) were treated with steroids. In a multivariate analysis, the use of steroids was associated with a trend towards increased hospital mortality (OR = 3.6; 95%CI: 0.98-13.6; P = 0.052). Nevertheless, patients using steroids were often more severely ill.

Martin-Loeches *et al*[31], in an international registry of the European Society of Intensive Care Medicine included 220 patients with suspected or confirmed H1N1, 77.7% on mechanical ventilation and 57.3% with steroid use at ICU admission. A higher incidence of hospital-acquired pneumonia was noted in patients receiving early steroid therapy. These patients also had a higher ICU mortality, but after adjusting for disease severity and other confounding variables, this effect was no longer present.

Kim *et al*[35] in a retrospective analysis of the data from 28 hospitals in South Korea identified 245 critically ill patients with H1N1 infection, 136 of them met criteria for ARDS. The crude 90-d mortality for the 107 (43.6%) patients who received steroids was higher than in the patients who did not received steroids, which was confirmed by propensity adjusted analysis. Patients on steroids also had longer duration of mechanical ventilation

Table 1 Main observational studies evaluating steroid use in influenza infection

Ref.	Study design	Population	Steroid regimen	Outcomes
Bourdreault *et al*[33]	Retrospective cohort	143 hematopoietic cell transplant patients with seasonal influenza	Prednisone < 1 mg/kg per day (low dose) or prednisone > 1 mg/kg per day (high dose)	Steroid use not associated with lower respiratory disease, hypoxemia, need for MV or death
Brun-Buisson *et al*[36]	Retrospective cohort	208 patients with ARDS due to H1N1 pneumonia, 83 receiving steroids	Hydrocortisone 270 mg/d (median) for 11 d (median)	Steroid was associated with mortality in crude analysis (33% *vs* 18%, HR = 2.4; 95%CI: 1.3-4.3; P = 0.004) and after propensity score-adjusted analysis (HR = 2.82; 95%CI: 1.5-5.4; P = 0.002) Early therapy (≤ 3 d of MV) associated with increased mortality Steroid associated with bacterial pneumonia and prolonged MV
Confalonieri *et al*[44]	Case report	One patient with ARDS due to H1N1 infection, not responding to antiviral therapy	Methylprednisolone 1 mg/kg per day	Clinical improvement
Cornejo *et al*[40]	Case report	Two patients with H1N1 that developed organizing pneumonia	Methylprednisolone 500 mg/d for 3 d	Clinical improvement
Diaz *et al*[37]	Multicenter, prospective cohort	372 patients with primary H1H1 pandemic pneumonia, 136 receiving steroids	Not reported	Corticosteroid therapy was not significantly associated with mortality (HR = 1.06; 95%CI: 0.626-1.801; P = 0.825) after a regression analysis adjusted for severity and potential confounding factors
Han *et al*[45]	Multicenter, retrospective cohort	83 patients with H1N1 pneumonia with hospitalar admission, 17 with early glucocorticoid treatment	Median dose of methylprednisolone equivalent of 50 mg/d (use for fever reduction) to 61 mg/d (use for pneumonia)	Early steroid treatment (< 72 h) was associated with development of critical disease compared with who received late (> 72 h) or no steroid treatment: 71% vs 39% (HR = 1.8; 95%CI: 1.2-2.8), after adjustment for confounding variables
Kim *et al*[35]	Multicenter, retrospective cohort and case-control study	245 patients with H1N1 infection, 107 with steroid treatment	Median dose of prednisolone equivalent of 75 mg/d	90-d mortality rate higher in steroids group (OR = 2.2; 95%CI: 1.03-4.71), after propensity score Higher mortality both in cohort (58% *vs* 27%; P < 0.001) and case-control study (54% *vs* 31%; P = 0.004) Steroid group more likely to have secondary bacterial pneumonia, invasive fungal infection and prolonged intensive care unit stay
Luyt *et al*[46]	Multicenter, prospective cohort study	37 survivors of ARDS due to H1N1 infection, 20 with steroid treatment	Not reported	No relationship between steroid use and muscle weakness at 1-yr post-ICU discharge
Martin-Loeches *et al*[31]	Multicenter, prospective cohort study	220 patients with H1N1 infection, 126 with steroid treatment at ICU admission	Minimal equivalent dose of 24 mg/d (methylprednisolone) or 30 mg/d (prednisone)	Early use of steroids was not significantly associated with mortality by Cox regression analysis adjusted for severity and confounding factors: HR = 1.3; 95%CI: 0.7-2.4; P = 0.4 Early steroid use associated with an increased rate of HAP (OR = 2.2; 95%CI: 1.0-4.8; P < 0.05) by Cox regression analysis Similar results observed when only patiens with ARDS were analyzed Patients who received early steroid therapy were sicker than who did not receive them according to SAPS 3 (55.9 ± 16.8 *vs* 49.0 ± 14.5; P = 0.001)
Quispe-Laime *et al*[47]	Case series	13 patients with suspected H1N1 pneumonia and ALI-ARDS diagnosis	Methylprednisolone 1 mg/kg per day (severe ARDS) or hydrocortisone 300 mg/d. Duration of 21.2 ± 6.1 d	Twelve patients improved lung function, were extubated and discharged alive from the ICU By day 7 of treatment patients experienced a significant improvement in lung injury and multiple organ dysfunction scores (P < 0.001)

ALI: Acute lung injury; ARDS: Acute distress respiratory syndrome; HAP: Hospital-acquired pneumonia; HR: Hazard ratio; ICU: Intensive care unit; MV: Mechanical ventilation; OR: Odds ratio; SAPS: Simplified acute physiology score.

and ICU stay, and more bacterial pneumonia or invasive fungal infections.

Brun-Buisson *et al*[36] evaluated 208 patients with severe H1N1 infections and ARDS in a multicenter study in France. Steroids were administered to 39.9% and, after use of several analytical techniques to adjust for differences in steroid-treated *vs* non-steroid-treated patients to compare clinical outcomes, the association between steroid therapy and death remained significant, a fact that was more pronounced in patients receiving early steroid therapy.

Diaz *et al*[37], in a multicenter cohort composed by 372-patients with primary viral pneumonia due to H1N1, with 136 patients (36.6%) received corticosteroids, did not found any association between steroid therapy and mortality.

A systematic review and meta-analysis[3] composed by nine cohort studies (n = 1405) and 14 case-control studies (n = 4700) showed an increased mortality with corticosteroid treatment in influenza H1N1 infection (cohort studies RR = 1.85; 95%CI: 1.46-2.33; $P < 0.00001$; case-control studies OR = 4.22; 95%CI: 3.10-5.76; $P < 0.00001$). Subgroup and sensitive analysis were consistent with each other, suggesting that steroid treatment is associated with higher mortality. Nonetheless, corticosteroid tends to be used in the sickest case-patients.

None of these studies provided data on mechanical ventilation parameters. Lung protective ventilation is the standard of care for ARDS patients[38], and lack of data regarding this issue implies a dose of uncertainty about a major factor in determining which determines clinical outcomes[39]. The timing and dose of corticosteroid therapy were also not controlled in the study, and no specific drug regimen has been suggested in this context. Actually, several administration regimens, dosage and therapy duration are described in different studies, resulting in high heterogeneous strategies, adding complexity to systematic analysis. Observational - in particular retrospective - studies are potentially susceptible to bias, due to a lack of control of confounder variables, heterogeneity due to clinical diversity, and the fact that severe patients are more likely to receive corticosteroids than mild cases. Currently a conclusive trial on corticosteroids in severe H1N1 infection would be difficult or even not possible to perform. As a result it is reasonable to conclude from the available evidence that corticosteroids failed to demonstrate any clinical impact in severe influenza infection and, in addition, the data points to potential harm.

Case reports suggested beneficial use in specific contexts, such as organizing pneumonia[40], post-viral inflammatory pneumonitis[41] and H1N1 pneumonia in a pregnant woman[42].

Interventional studies

There is only one clinical trial addressing corticosteroid use in H1N1 influenza virus treatment. Wang *et al*[43] enrolled 38 patients with H1N1 pneumonia undergoing mechanical ventilation to be randomized to receive adjuvant treatment of corticosteroid either with sirolimus or without sirolimus for 14 d. In the sirolimus group, there was a shorter time spent on mechanical ventilation (7 d *vs* 15 d; P = 0.03), greater PaO_2-FiO_2 values on days 3 and 7 compared to the non-sirolimus group and improved SOFA score on day 3 and day 7. Sirolimus, as a mTOR inhibitor, could potentiate corticosteroid effect by limiting inflammatory cytokine production. The corticosteroid effect per se was not addressed in this small open-label randomized controlled trial as every patient enrolled received corticosteroids. As a consequence, no harmful or beneficial effect of steroids in H1N1 pneumonia can be inferred.

Critical analysis

Heterogeneity of published data regarding study design, population demographics, severity of illness, dosing, type and timing of corticosteroids administered constitute an important limitation for drawing robust conclusions. However, it is reasonable to admit that, as it was not found any advantage of corticosteroid therapy in so diverse conditions, such beneficial effects do not exist at all. Recent insights on a decrease in cortisol breakdown during critical illness questions the classic concept of adrenal failure with low cortisol production and constitutes a molecular argument against the use of corticosteroids as standard of care for patients with critical illness: The increased cortisol circulating levels and tissue activity make an additional synthetic corticosteroid dose either redundant or excessive and not devoid of deleterious effects.

Finally, it is reasonable to conclude that corticosteroids failed to demonstrate any beneficial effects in the treatment of patients with severe influenza infection. Its administration is likely to increase overall mortality and such trend is consistent regardless of the quality as well as the sample size of studies. Moreover it was shown that corticosteroids might be associated with higher incidence of hospital-acquired pneumonia and longer duration of mechanical ventilation and ICU stay. Thus its current use in Severe Influenza pneumonia should be restricted to selected cases and in the setting of clinical trials.

REFERENCES

1 **Ramsey CD**, Kumar A. Influenza and endemic viral pneumonia. *Crit Care Clin* 2013; **29**: 1069-1086 [PMID: 24094391 DOI: 10.1016/j.ccc.2013.06.003]

2 **Dunning J**, Openshaw P. Severe Influenza: Clinical Features and Treatment Options. *Curr Resp Med Rev* 2012; **1**: 208-217 [DOI: 10.2174/157339812800493223]

3 **Zhang Y**, Sun W, Svendsen ER, Tang S, MacIntyre RC, Yang P, Zhang D, Wang Q. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. *Crit Care* 2015; **19**: 46 [PMID: 25888424 DOI: 10.1186/s13054-015-0764-5]

4 **Póvoa P**, Salluh JI. What is the role of steroids in pneumonia therapy? *Curr Opin Infect Dis* 2012; **25**: 199-204 [PMID: 22156902 DOI: 10.1097/QCO.0b013e32834f44c7]

5 **Hendrickson CM**, Matthay MA. Viral Pathogens and Acute Lung Injury: Investigations Inspired by the SARS Epidemic and the 2009 H1N1 Influenza Pandemic. *Semin Respir Crit Care Med* 2013; **34**:

475-486 [PMID: 23934716 DOI: 10.1055/s-0033-1351122]
6 **Hilleman MR**. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. *Vaccine* 2002; **20**: 3068-3087 [PMID: 12163258 DOI: 10.1016/S0264-410X(02)00254-2]
7 **Potter CW**. A history of influenza. *J Appl Microbiol* 2001; **91**: 572-579 [PMID: 11576290 DOI: 10.1046/j.1365-2672.2001.01492.x]
8 **Dawood FS**, Iuliano AD, Reed C, Meltzer MI, Shay DK, Cheng PY, Bandaranayake D, Breiman RF, Brooks WA, Buchy P, Feikin DR, Fowler KB, Gordon A, Hien NT, Horby P, Huang QS, Katz MA, Krishnan A, Lal R, Montgomery JM, Mølbak K, Pebody R, Presanis AM, Razuri H, Steens A, Tinoco YO, Wallinga J, Yu H, Vong S, Bresee J, Widdowson MA. Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. *Lancet Infect Dis* 2012; **12**: 687-695 [PMID: 22738893 DOI: 10.1016/S1473-3099(12)70121-4]
9 **Webb SA**, Pettilä V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, Cretikos M, Davies AR, Finfer S, Harrigan PW, Hart GK, Howe B, Iredell JR, McArthur C, Mitchell I, Morrison S, Nichol AD, Paterson DL, Peake S, Richards B, Stephens D, Turner A, Yung M. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009; **361**: 1925-1934 [PMID: 19815860 DOI: 10.1056/NEJMoa0908481]
10 **Jain S**, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, Sugerman DE, Druckenmiller JK, Ritger KA, Chugh R, Jasuja S, Deutscher M, Chen S, Walker JD, Duchin JS, Lett S, Soliva S, Wells EV, Swerdlow D, Uyeki TM, Fiore AE, Olsen SJ, Fry AM, Bridges CB, Finelli L. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009; **361**: 1935-1944 [PMID: 19815859 DOI: 10.1056/NEJMoa0906695]
11 **Konter J**, Baez E, Summer RS. Obesity: "priming" the lung for injury. *Pulm Pharmacol Ther* 2013; **26**: 427-429 [PMID: 22449512 DOI: 10.1016/j.pupt.2012.03.003]
12 **Stapleton RD**, Dixon AE, Parsons PE, Ware LB, Suratt BT. The association between BMI and plasma cytokine levels in patients with acute lung injury. *Chest* 2010; **138**: 568-577 [PMID: 20435656 DOI: 10.1378/chest.10-0014]
13 **Mauad T**, Hajjar LA, Callegari GD, da Silva LF, Schout D, Galas FR, Alves VA, Malheiros DM, Auler JO, Ferreira AF, Borsato MR, Bezerra SM, Gutierrez PS, Caldini ET, Pasqualucci CA, Dolhnikoff M, Saldiva PH. Lung pathology in fatal novel human influenza A (H1N1) infection. *Am J Respir Crit Care Med* 2010; **181**: 72-79 [PMID: 19875682 DOI: 10.1164/rccm.200909-1420OC]
14 **Giannella M**, Alonso M, Garcia de Viedma D, Lopez Roa P, Catalán P, Padilla B, Muñoz P, Bouza E. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. *Clin Microbiol Infect* 2011; **17**: 1160-1165 [PMID: 20946412 DOI: 10.1111/j.1469-0691.2010.03399]
15 **Katzung, BG**, Masters, SB, Trevor AJ. Adrenocorticosteroids & Adrenocortical Antagonists. Basic & clinical pharmacology. New York: McGraw-Hil, 2012: 697-713
16 **Mckay LI**, Cidlowski JA. Pharmacokinetics of Corticosteroids. In: Kufe DW, Pollock RE WR, editors. Holland-Frei Cancer Medicine 6th edition. 6th ed. Hamilton (ON): BC Decker; 2003
17 **Marik PE**. Critical illness-related corticosteroid insufficiency. *Chest* 2009; **135**: 181-193 [PMID: 19136406 DOI: 10.1378/chest.08-1149]
18 **Boonen E**, Vervenne H, Meersseman P, Andrew R, Mortier L, Declercq PE, Vanwijngaerden YM, Spriet I, Wouters PJ, Vander Perre S, Langouche L, Vanhorebeek I, Walker BR, Van den Berghe G. Reduced cortisol metabolism during critical illness. *N Engl J Med* 2013; **368**: 1477-1488 [PMID: 23506003 DOI: 10.1056/NEJMoa1214969]
19 **Selye H**. A syndrome produced by diverse nocuous agents. 1936. *J Neuropsychiatry Clin Neurosci* 1998; **10**: 230-231 [PMID: 9722327]
20 **Widmer IE**, Puder JJ, König C, Pargger H, Zerkowski HR, Girard J, Müller B. Cortisol response in relation to the severity of stress and illness. *J Clin Endocrinol Metab* 2005; **90**: 4579-4586 [PMID: 15886236 DOI: 10.1210/jc.2005-0354]
21 **Carrasco GA**, Van de Kar LD. Neuroendocrine pharmacology of stress. *Eur J Pharmacol* 2003; **463**: 235-272 [PMID: 12600714 DOI: 10.1016/j.bbr.2011.01.038]
22 **Bornstein SR**, Engeland WC, Ehrhart-Bornstein M, Herman JP. Dissociation of ACTH and glucocorticoids. *Trends Endocrinol Metab* 2008; **19**: 175-180 [PMID: 18394919 DOI: 10.1016/j.tem.2008.01.009]
23 **Vermes I**, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. *J Clin Endocrinol Metab* 1995; **80**: 1238-1242 [PMID: 7714094 DOI: 10.1210/jcem.80.4.7714094]
24 **Bornstein SR**, Chrousos GP. Clinical review 104: Adrenocorticotropin (ACTH)- and non-ACTH-mediated regulation of the adrenal cortex: neural and immune inputs. *J Clin Endocrinol Metab* 1999; **84**: 1729-1736 [PMID: 10323408 DOI: 10.1210/jcem.84.5.5631]
25 **Neary N**, Nieman L. Adrenal insufficiency: etiology, diagnosis and treatment. *Curr Opin Endocrinol Diabetes Obes* 2010; **17**: 217-223 [PMID: 20375886 DOI: 10.1097/MED.0b013e328338f608]
26 **Falagas ME**, Vouloumanou EK, Baskouta E, Rafailidis PI, Polyzos K, Rello J. Treatment options for 2009 H1N1 influenza: evaluation of the published evidence. *Int J Antimicrob Agents* 2010; **35**: 421-430 [PMID: 20185273 DOI: 10.1016/j.ijantimicag.2010.01.006]
27 **Kumar A**, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, Stelfox T, Bagshaw S, Choong K, Lamontagne F, Turgeon AF, Lapinsky S, Ahern SP, Smith O, Siddiqui F, Jouvet P, Khwaja K, McIntyre L, Menon K, Hutchison J, Hornstein D, Joffe A, Lauzier F, Singh J, Karachi T, Wiebe K, Olafson K, Ramsey C, Sharma S, Dodek P, Meade M, Hall R, Fowler RA. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009; **302**: 1872-1879 [PMID: 19822627 DOI: 10.1001/jama.2009.1496]
28 **Domínguez-Cherit G**, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, Poblano-Morales M, Baltazar-Torres JA, Bautista E, Martinez A, Martinez MA, Rivero E, Valdez R, Ruiz-Palacios G, Hernández M, Stewart TE, Fowler RA. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2009; **302**: 1880-1887 [PMID: 19822626 DOI: 10.1001/jama.2009.1536]
29 **Brouwer MC**, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2015; **9**: CD004405 [PMID: 26362566]
30 **Ewald H**, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV infection. *Cochrane Database Syst Rev* 2015; **4**: CD006150 [PMID: 25835432 DOI: 10.1002/14651858.CD006150.pub2]
31 **Martin-Loeches I**, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, Chiche JD, Barahona D, Villabon M, Balasini C, Pearse RM, Matos R, Rello J. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. *Intensive Care Med* 2011; **37**: 272-283 [PMID: 21107529 DOI: 10.1007/s00134-010-2078-z]
32 **Ison MG**. Adjuvant immunosuppression in the management of severe influenza: friend or foe? *Crit Care Med* 2014; **42**: 457-459 [PMID: 24434448 DOI: 10.1097/CCM.0b013e3182a63779]
33 **Boudreault AA**, Xie H, Leisenring W, Englund J, Corey L, Boeckh M. Impact of corticosteroid treatment and antiviral therapy on clinical outcomes in hematopoietic cell transplant patients infected with influenza virus. *Biol Blood Marrow Transplant* 2011; **17**: 979-986 [PMID: 20870025 DOI: 10.1016/j.bbmt.2010.09.014]
34 **Xi X**, Xu Y, Jiang L, Li A, Duan J, Du B. Hospitalized adult patients with 2009 influenza A(H1N1) in Beijing, China: risk factors for hospital mortality. *BMC Infect Dis* 2010; **10**: 256 [PMID: 20799934 DOI: 10.1186/1471-2334-10-256]
35 **Kim SH**, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, Lee HB,

Lim CM, Koh Y. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. *Am J Respir Crit Care Med* 2011; **183**: 1207-1214 [PMID: 21471084 DOI: 10.1164/rccm.201101-0110OC]

36 **Brun-Buisson C**, Richard JC, Mercat A, Thiébaut AC, Brochard L. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2011; **183**: 1200-1206 [PMID: 21471082 DOI: 10.1164/rccm.201101-0135OC]

37 **Diaz E**, Martin-Loeches I, Canadell L, Vidaur L, Suarez D, Socias L, Estella A, Gil Rueda B, Guerrero JE, Valverdú-Vidal M, Vergara JC, López-Pueyo MJ, Magret M, Recio T, López D, Rello J, Rodriguez A. Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. *J Infect* 2012; **64**: 311-318 [PMID: 22240033 DOI: 10.1016/j.jinf.2011.12.010]

38 **Slutsky AS**, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2014; **370**: 980 [PMID: 24597883 DOI: 10.1056/NEJMc1400293]

39 **Matthay MA**, Liu KD. Con: corticosteroids are not indicated for treatment of acute lung injury from H1N1 viral pneumonia. *Am J Respir Crit Care Med* 2011; **183**: 1127-1128 [PMID: 21531953 DOI: 10.1164/rccm.201103-0395ED]

40 **Cornejo R**, Llanos O, Fernández C, Carlos Díaz J, Cardemil G, Salguero J, Luengo C, Tobar E, Romero C, Gálvez LR. Organizing pneumonia in patients with severe respiratory failure due to novel A (H1N1) influenza. *BMJ Case Rep* 2010; **2010**: [PMID: 22767562 DOI: 10.1136/bcr.02.2010.2708]

41 **Roberts C**, Nirmalan M, O'Shea S. Steroid-sensitive post-viral inflammatory pneumonitis (PVIP). *Am J Respir Crit Care Med* 2010; **182**: 1089-1090 [PMID: 20947911]

42 **Djibré M**, Berkane N, Salengro A, Ferrand E, Denis M, Chalumeau-Lemoine L, Parrot A, Mayaud C, Fartoukh M. Non-invasive management of acute respiratory distress syndrome related to Influenza A (H1N1) virus pneumonia in a pregnant woman. *Intensive Care Med* 2010; **36**: 373-374 [PMID: 19820915 DOI: 10.1007/s00134-009-1684-0]

43 **Wang CH**, Chung FT, Lin SM, Huang SY, Chou CL, Lee KY, Lin TY, Kuo HP. Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. *Crit Care Med* 2014; **42**: 313-321 [PMID: 24105455 DOI: 10.1097/CCM.0b013e3182a2727d]

44 **Confalonieri M**, D'Agaro P, Campello C. Corticosteroids do not cause harmful increase of viral load in severe H1N1 virus infection. *Intensive Care Med* 2010; **36**: 1780-1781 [PMID: 20631982 DOI: 10.1007/s00134-010-1964-8]

45 **Han K**, Ma H, An X, Su Y, Chen J, Lian Z, Zhao J, Zhu BP, Fontaine RE, Feng Z, Zeng G. Early use of glucocorticoids was a risk factor for critical disease and death from pH1N1 infection. *Clin Infect Dis* 2011; **53**: 326-333 [PMID: 21810744 DOI: 10.1093/cid/cir398]

46 **Luyt CE**, Combes A, Becquemin MH, Beigelman-Aubry C, Hatem S, Brun AL, Zraik N, Carrat F, Grenier PA, Richard JC, Mercat A, Brochard L, Brun-Buisson C, Chastre J. Long-term outcomes of pandemic 2009 influenza A(H1N1)-associated severe ARDS. *Chest* 2012; **142**: 583-592 [PMID: 22948576 DOI: 10.1378/chest.12-0917]

47 **Quispe-Laime AM**, Bracco JD, Barberio PA, Campagne CG, Rolfo VE, Umberger R, Meduri GU. H1N1 influenza A virus-associated acute lung injury: response to combination oseltamivir and prolonged corticosteroid treatment. *Intensive Care Med* 2010; **36**: 33-41 [PMID: 19924393 DOI: 10.1007/s00134-009-1727-6]

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