

To use or not to use corticosteroids for pneumonia? A clinician's perspective

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ABSTRACT: *To use or not to use corticosteroids for pneumonia? A clinician's perspective. M. Confalonieri, M. Kodric, M. Santagiuliana, C. Longo, M. Biolo, R. Cifaldi, C. Torregiani, M. Jevnikar.*

The use of corticosteroids in the management of pneumonia is still a controversial issue. The physicians in daily clinical practice often use corticosteroids in patients with pneumonia for different reasons all over the world. As an example of real life is the frequent use of corticosteroids to treat patients with pneumonia due to H1N1 pandemic influenza in spite of WHO' statements that clearly discouraged this therapy. In fact, the literature up to august 2012 reported a total of 6,650 patients with pneumonia due to H1N1 virus infection (of whom 2,515 were ICU patients): corticosteroids were used with various dose regimens in 2404 patients (37.8%). The attitude of international guidelines on pneumonia in using steroids do not help the clinician to clearly choice when and how to treat pneumonia with steroids. However, stress doses of corti-

costeroids are suggested by some major guidelines on community-acquired pneumonia in case of severe episodes with sepsis. To date, there are 10 randomised controlled trials assessing the effectiveness of corticosteroids for community-acquired pneumonia globally involving 1090 participants . Most of the trials adopted stress doses of glucocorticoids for 4-7 days. The evidence from these trials taken separately is weak due to limitations of the studies themselves, but a Cochrane review and a systematic review found benefit using prolonged low doses of glucocorticoids in severe community-acquired pneumonia. Moreover, such a strategy decreases vasopressor dependency and appears to be safe. Nevertheless, larger trials with more patients and clinically important end-points were claimed to provide robust evidence. Finally, infection surveillance is critical in patients treated with corticosteroids, and to prevent the rebound phenomenon, the drug should be weaned slowly.

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A long-standing debate for a complex dilemma

Pneumonia is one of the most common infectious diseases addressed by clinicians. It remains an important cause of morbidity and mortality, with significant economical and social cost [1]. To use or not to use corticosteroids in the management of patients with pneumonia is a long-standing dilemma in the scientific literature with no definitive final response currently [2, 3]. From the half of the past century to date there were a number of clinical case reports, observational studies, controlled trials, and systematic reviews on the use of systemic corticosteroids in patients with pneumonia, but the scientific debate is still open [4-16]. There is no clear evidence regarding regular use of corticosteroids for each pneumonia, but also there is no evidence to suggest avoiding steroids for any pneumonia. Steroids potentially modulate the marked and persistent activation of the immune system in pneumonia, but the results of different studies on corticosteroids for pneumonia are controversial. Moreover, steroids may have different effects according to the dose regimen. The first

statement to be made is that "to use or not to use corticosteroids for pneumonia?" is not a simple question. A part the lack of convincing scientific evidence from the published studies, the problem is complex because pneumonia is not a homogeneous and simple disease, and corticosteroids, in spite of their extended use, are not elementary drugs. Pneumonia may be a community-acquired or a hospital-acquired disease, affecting previously healthy people or with chronic illness and/or defects of the immune system. The microbial etiology of pneumonia is often not characterized at time of diagnosis, and the host response to the infection not always predictable [17]. Prognosis of pneumonia varies considerably from a mild self-limiting disease to a severe one becoming to a life-threatening condition. Corticosteroids can modulate inflammation, suppress the immune system, influence carbohydrate metabolism, protein catabolism, electrolyte balance, and regulate stress response. Moreover, corticosteroids may have genomic and non- genomic effects according to type of drug, administration schemes, and doses. The present review aims to discuss the question "to use

or not to use corticosteroids for this patient with pneumonia?" from a clinician's perspective, as clinicians face this question in their daily practice. In the past two decades [18-20], with the availability of biomarker assays, longitudinal measurements have shown that persistent (in place of short-lived) elevation of circulating concentrations of inflammatory cytokines over time (dysregulated systemic inflammation) is the central pathogenetic process contributing to morbidity and mortality in community-acquired pneumonia, sepsis, and acute respiratory distress syndrome. At cellular level, patients with dysregulated inflammation have inadequate glucocorticoid receptor-mediated downregulation of inflammatory transcription factor nuclear factor- κ B, despite often having increased concentrations of circulating cortisol (systemic inflammation-associated glucocorticoid resistance). Systemic inflammation - associated glucocorticoid resistance can be reversed by increasing glucocorticoid receptor α activation with quantitatively adequate and prolonged glucocorticoid supplementation. In patients with sepsis and ARDS, much evidence supports a strong association between prolonged downregulation, induced by glucocorticoid treatment, of the inflammatory response and improvement in organ physiology [21, 22]. Even short treatment with glucocorticoid is associated with downregulation of glucocorticoid receptor concentrations in most cell types and adrenal insufficiency; without 6-9 days' tapering, rebound systemic inflammation is common and associated with substantial clinical deterioration [23, 24]. So, the therapeutic consequences of these pathophysiological observations should be that corticosteroids are used only as a "stress dose" (prolonged low doses until resolution of systemic inflammation) [25]. In this review we avoid discussing experimental and pathophysiological data, but concentrate on the available clinical evidence.

The use of corticosteroids for pneumonia in the "real life": the case of H1N1 virus pneumonia

The off-label use of corticosteroids by clinicians is widespread and diffused both within the hospital and outpatient clinics. Corticosteroids may be used as a rescue therapy in critical care, but also are familiar drugs to any physician in diverse clinical conditions. In real-life, pneumonia is sometimes treated also with IV or oral corticosteroids and/or oral non-steroidal anti-inflammatory drugs (NSAIDs) to reduce the lung tissue inflammation, regardless of the type of pneumonia and organism or type of irritation or foreign substances involved. It is quite difficult to determine the proportion of patients with CAP currently treated with corticosteroids in the real life, not considering the differences among locations of care, specialisation of the physicians, criteria to evaluate severity of pneumonia, microbiologic etiology, and so on. Some trials on the efficacy of glucocorticoids in CAP have clearly permitted the use of steroids also in the placebo arm for rescue purpose or in case of sepsis, so confounding the interpretation of the results on a

intention-to-treat basis [12]. As an example of the general confusion surrounding this issue, is the case of the H1N1 virus influenza. The World Health Organization (WHO) clearly discouraged treatment with steroids during the recent H1N1 virus pandemic [26], but several large observational studies from real-life reported the use of corticosteroids in a consistent portion of patients with pneumonia, particularly the severe ones admitted to Intensive Care Unit (ICU) (table 1) [27-49]. The total number of patients reported in these studies was 6,650 (of whom 2,515 were ICU patients), corticosteroids were used with various or unknown dose regimen in 2404 patients. Some patients were treated with steroids being affected by chronic obstructive pulmonary disease (COPD) or asthma, but most of them had pneumonia. Noticeably, the percentage of patients admitted to hospital, and then treated with corticosteroids was unexpectedly high in the cohort population of observational studies on H1N1 virus infection (37.8%). The reported effects of corticosteroids during the 2009 H1N1 pandemic were varied, but no prospective randomised study was performed. The various results reported in these cohort studies and case series reflect that corticosteroids are broadly used, more than the amount of evidence about its effectiveness on viral pneumonia. Registries and retrospective cohorts usually aim at describing the natural history of a disease in the real life and not at investigating interventions like only randomized double-blind trials can do. There are numerous examples of interventions found to be harmful in cohort studies and not in subsequent randomised trials, such as the use of the Swan Ganz catheter [50]. Nevertheless, there was no clear evidence in the literature for increased mortality or survival with corticosteroids, neither in real life. The common practice in real life seems to promote the use of corticosteroids for severe pneumonia and critically ill patients more than in mild-to-moderate cases, but the decision to adopt or not this adjunctive therapy for pneumonia cannot be based only on observational study reports [51, 52].

The recommendations of the international guidelines

The most renowned guidelines by international and national scientific organisations recognize evidence-based methodology to cover the principal aspects of pneumonia care. Whilst most societies have restricted their guidelines to Community-Acquired Pneumonia (CAP), the ATS-IDSA (American Thoracic Society/Infectious Diseases Society of America) distinguished CAP from Hospital-Acquired Pneumonia/Health Care-Acquired Pneumonia/Ventilator-Acquired Pneumonia (HAP/HCAP/VAP) by mean of two different consensus statements [53, 54], while the European Respiratory Society (ERS) addresses all aspects of care for respiratory tract infections both in the community and hospital settings [55]. The main objective of these statements is to standardize diagnosis and definitions, and to rationalise antibiotic empiric treatment based on the prevalence of different

Table 1. - Observational studies reporting the use of corticosteroids in H1N1-virus infection

1st Author, Country	CS treated/all patients	Dose regimen	CS outcome	CS Adverse effects	Indications
Brun-Buisson, France, Switzerland	83/208	270 mg/d HC for 11 days	Steroids more deaths, (33.7 vs.16.8%)	Unknown/NA	ARDS/Pneumonia
Domínguez-Cherit, Mexico	40/52	Unknown/NA	Unknown/NA	Unknown/NA	Unknown/NA
Kim, Korea	107/245	Unknown/NA	90-d mortality 54% steroids vs 31% non-steroid group	Unknown/NA	Lower tract infections, pneumonia, ARDS
Linko, Finland	72/132	Stress dose	No difference in mortality albeit steroids were used in more severe patients	Unknown/NA	Acute respiratory failure, Pneumonia/ARDS
Han, China	46/83	Various	Increased rate of critical illness/death	NA	Pneumonia
Perez-Padilla, Mexico	7/18	HC300 mg/day or MP60 mg/day	3 survived 4 died (p=0.32)	Unknown/NA	Pneumonia
Díaz, Spain	136/372	Unknown/NA	Unchanged mortality-LoS	Unknown/NA	Pneumonia
Kumar, Canada	85/168	Unknown/NA	Unknown/NA	Unknown/NA	ARDS
Jain, USA	86/239	Unknown/NA	Unknown/NA	Unknown/NA	Comorbidities (e.g. COPD)
Gomez-Gomez, Mexico	16/50	Unknown/NA	Unknown/NA	Unknown/NA	Pneumonia
Kidd, UK	1/1	MP140 mg→ 30 mg qds	1 survived	None	Pneumonia
Chang, Taiwan	13/48	Unknown/NA	Unknown/NA	Unknown/NA	Respiratory illness
Quispe-Laime, Argentina	13/13	HC 300 mg/d or MP 1 mg/kg/day for 21 days	12/13 survived	None	Pneumonia/ ARDS/severe sepsis
Yang, China	1487/3066	NA	NA	NA	Pneumonia
Myles, UK	302/1083	Unknown/NA	CS reduced rate of critical illness/deaths in asthmatics	Unknown/NA	Asthma, COPD, Pneumonia
Lee, Korea	17/116	10 mg/kg/d MP for 1w tapering	17/17 survived	None	Pneumonia/ALI-ARDS
Martin-Loeches, Spain/Brazil/Portugal/France/Argentina/UK/Colombia/Ecuador	126/220	>24 mg/d MP, >30 mg/d P, diverse duration	NA	HAP 26.2% in CS versus 13.8%	Pneumonia, ARDS, Asthma, COPD
Sun, China	12/18	Unknown/NA	Unknown/NA	Unknown/NA	ARDS
Chien, Taiwan	21/96	Different dosages	CS correlates with death	Bacterial infections	Pneumonia
Rello, Spain	11/32	Unknown/NA	Unknown/NA	Unknown/NA	Unknown/NA
CDC, USA	5/10	Unknown/NA	Unknown/NA	Unknown/NA	ARDS
Webb, Australia/NZ	91/494	Unknown/NA	Unknown/NA	Unknown/NA	ARDS/severe pneumonia
Confalonieri, Italy	8/8	MP 1 mg/kg for 7-21 day	8/8 survived 2 underwent invasive MV	Hyperglycemia 50%, infections 37%	Severe Pneumonia

NA = Not Available; CS = corticosteroids; HC = Hydrocortisone; LoS = Length of stay in Hospital; MP = MethylPrednisolone; P = Prednisone; COPD = Chronic Obstructive Pulmonary Disease; ARDS = Acute Respiratory Distress Syndrome; ALI = Acute Lung Injury; HAP = Hospital Acquired Pneumonia.

causative organisms as well as disease severity. So, all guidelines for the management of adult pneumonia pay little or no attention to other treatments than antibiotics, corticosteroids included. Table 2 shows the different attitude towards the

use of corticosteroids for pneumonia in the most cited guidelines [53-56]. The recommendations regarding the use of corticosteroids in pneumonia are different in diverse guidelines, and this fact is unsurprising giving that there is a lack of quality

Table 2. - Recommendations regarding the use of corticosteroids for pneumonia in the most recent principal guidelines

Guidelines	ATS/IDSA	ATS/IDSA	ERS/ESCMID	BTS
Type of pneumonia	CAP	HAP-HCAP-VAP	Lower respiratory tract infections	CAP
Year	2007	2005	2011	2009
Use of corticosteroids recommended?	Yes, stress-dose (hydrocortisone 200-300 mg/d)	No mention	No	Not routinely
When	Severe pneumonia with occult adrenal insufficiency	NA	Corticosteroids are not recommended for pneumonia, unless supportive care for sepsis	Steroids are not recommended in routine treatment of severe CAP
Grade of recommendation, level of evidence	B II	NA	A III	A I-II

ATS = American Thoracic Society; IDSA = Infectious Disease Society of America; ERS = European Respiratory Society; ESCMID = European Society for Clinical Microbiology and Infectious Diseases; BTS = British Thoracic Society; CAP = Community Acquired Pneumonia; HAP = Hospital Acquired Pneumonia; HCAP = Health-Care Associated Pneumonia; VAP = Ventilator Associated Pneumonia; NA = Not applicable.

evidence behind the majority of the guideline recommendations, as Woodhead addressed in a recent Editorial [57]. In fact, only between 6.5% and 21% of guidelines are based on “best-level” evidence [57]. Obviously, when guidelines differ it is often for lack of robust evidence, such as the case of corticosteroids for pneumonia. Nevertheless, the only recommendation for corticosteroid therapy for patients with pneumonia is in case of severe CAP with sepsis [53, 56]. No other recommendation for the practical clinician is forthcoming to date from guidelines.

Community-acquired and hospital acquired pneumonia trials and corticosteroids use

CAP

All the randomised controlled trials (RCTs) on the use of corticosteroids for pneumonia were performed in patients with CAP. Until the last decade of the past century there were influent trials on the use of high doses of corticosteroids for 48 hours showing negative effects in patients with sepsis, also due to pneumonia. Subsequently, new knowledge of the mechanisms of corticosteroids stimulate new clinical studies with corticosteroids based on stress doses (prolonged low doses) in patients with sepsis, ARDS, and also pneumonia [58]. It was recognised that only a stress dose can activate the genomic effect of steroids. Moreover, the early interruption of glucocorticoids may be dangerous because of a rebound effect on pro-inflammatory cytokines [23]. To date, there are 10 randomised controlled trials (RCTs) assessing the effectiveness of corticosteroids for community-acquired pneumonia involving 1090 participants (table 3). Most of the trials adopted stress doses of glucocorticoids for 4-7 days. The evidence from these RCTs taken separately is weak due to limitations of the studies

themselves (different dose regimens, primary end-points not clinically important, use of corticosteroids as rescue therapy also for controls, diverse pneumonia severity, small population study). Large trials with more patients and clinically important end-points are needed to provide robust evidence. Nevertheless, actually the overall effect of low prolonged dose of corticosteroids is more beneficial for patients with severe pneumonia (short length of hospital stay and duration of mechanical ventilation, time to improvement of oxygenation and chest X-ray, less incidence of severe sepsis and multiple organ failure syndrome) [4, 10-13, 25]. If corticosteroids are administered, infection surveillance, avoidance of neuromuscular blockers, and gradual taper of corticosteroids are recommended.

HAP-VAP

There were no studies to date specifically addressing to use corticosteroids for patients with HAP. Some studies tested the hypothesis that corticosteroids may reduce or increase the risk to develop hospital acquired pneumonia, especially ICU-acquired ones, but the results were conflicting because of the several flaws due to different dose regimens, study population, standardised interventions, and so on. As an example is the case of severe trauma. Pneumonia is a looming threat for trauma patients, the overall incidence of post-traumatic pneumonia is 40-60%, mainly in patients with traumatic brain injury. Early post-traumatic pneumonia may increase the duration of mechanical ventilation, hospitalisation and the risk of death. The MRC CRASH trial (corticosteroid administration after significant head injury) is a large international double-blind randomised placebo-controlled trial of the effect of early administration of a 48-h infusion of methylprednisolone on the risk of death

Table 3. - Randomised Controlled Trials (RCTs) on corticosteroids for CAP

1st Author, year	# patients, Primary Outcome	CS dose regimen	Severity of pneumonia	Results	Study limitations
Cao, 2007 [ref. 9]	120, period until symptoms are resolved	Budesonide	Mild to moderate pneumonia	CS reduces the duration of symptoms and number relapses	Small sample size, bias in study design
Confalonieri, 2005 [ref. 4]	56, PaO ₂ :FiO ₂ improvement	200 mg HC bolus, then 240 mg/day HC for 7 day	Severe pneumonia (ATS 1991), most of them with sepsis	Earlier PaO ₂ :FiO ₂ improvement with CS	Early interruption for more deaths in the placebo arm
van Woensel, 2003 [ref. 8]	85, duration of MV	IV DEX 0.15 mg/kg 6-hourly for 48 hours	Mild pneumonia, bronchiolitis	CS Increased LoS, need for MV increased	Several drop-outs or losses to follow up
Marik, 1993 [ref. 5]	30, mortality, ICU LoS, and serum TNFalpha level	10 mg/kg of hydrocortisone or placebo IV 30 min-prior to starting antibiotic therapy	Severe pneumonia	CS reduced LoS and duration of MV	Very short duration interventional therapy with CS (possible rebound)
McHardy, 1972 [ref. 6]	126, time to clinical resolution	20 mg/day P	Mild	No difference between groups	Small sample size, bias in study design
Fernandez-Serrano, 2011 [ref. 11]	56, requirement for MV and PaO ₂ :FiO ₂ improvement	Bolus iv 200mg MP then 20 mg/6 h for 3 days, then 20 mg/12 h for 3 days, and finally 20 mg/day for another 3 days	Severe pneumonia with ALI	CS reduced need for MV (not significant) and improved PaO ₂ :FiO ₂ significantly earlier than placebo	Small sample size
Sabry, 2011 [ref. 13]	80, PaO ₂ :FIO ₂ > 300 or >100 than study entry, and reduced septic shock	Loading dose 200 mg over 30 min, followed by 300 mg/day for 7 days	Intubated ICU-patients with severe pneumonia	CS significantly improved PaO ₂ :FIO ₂ and SOFA score at day 7	Small sample size, NIV was not used for weaning
Mikami, 2007 [ref. 7]	31, days to normalisation of SpO ₂	40 mg/d P IV for 3 days	Moderate and severe pneumonia	CS did not faster SpO ₂ normalization, but shortened antibiotic duration	Small sample size, open label study design
Snijders, 2010 [ref. 12]	213, clinical cure at day 7	40 mg P IV for 7 days	Mild-to-severe hospitalized patients	Primary end-point not reached	Mainly mild pneumonia, possibility to receive CS also for controls
Meijvis, 2011 [ref. 10]	304, length of hospital stay	iv DEX (5 mg once a day) for 4 days	Mild-to-severe (PSI I--V)	LoS reduction with CS	Possible use of CS in case of sepsis with bias analysis, CS effects not evaluated if need for MV

CS = corticosteroids; P = prednisone; MP = Methylprednisolone; HC = Hydrocortisone; DEX = Desamethasone; LoS = Length of hospital stay; MV = mechanical ventilation; SpO₂ = pulse oxymetry.

and disability after head injury [59]. The risk of death and severe disability was higher in the corticosteroid group than in the placebo group. Another more recent RCT in ICU- patients with severe traumatic brain injury used stress doses of hydrocortisone (continuous infusion iv 200 mg/d for 5 days, followed by 100 mg on day 6 and 50 mg on day 7)[60]. This multicentre French study showed that in intubated trauma patients, the use of an intravenous stress-dose of hydrocortisone, compared with placebo, resulted in a decreased risk of hospital-acquired pneumonia. Another very recent observational cohort study [61] performed in a single ICU where systemic methylprednisolone was given for several reasons was contrasting, showed an in-

creased development of ICU-acquired pneumonia in patients previously treated with steroids. In adjusted analysis, there was a higher risk of death with steroid use among patients with lower baseline organ dysfunction scores (P=0.05), and among those without bacteremia (P=0.03) or acute respiratory distress syndrome (P=0.03). The conclusion for the clinical practice from the conflicting results of diverse trials may be difficult, but some caveats could be picked up. The use of short-time high doses of corticosteroids should be discouraged in ICU-patients because it is harmful, but a monitored prolonged low dose regimen can be beneficial in selected case with severe sepsis and Adult Respiratory Distress Syndrome (ARDS) [62].

Mild-to-moderate pneumonia or only severe pneumonia?

The definition of severe pneumonia has not yet reached a general consensus. So, different studies on corticosteroids for CAP adopted diverse definition of severity. Nevertheless, most of the patients treated with corticosteroids in RCTs had severe pneumonia with need for ICU admission and/or mechanical ventilation. Among the ten RCTs on corticosteroids in CAP, some were dedicated to patients with severe pneumonia and others included a number of patients with mild and moderate pneumonia. The large Dutch study by Snijders and colleagues [12] found no evidence of efficacy for prednisolone 40mg once a day for a week in hospitalised CAP patients without severe sepsis, whilst the study by Meijvis *et al* [10] showed that a 4 day treatment with dexamethasone 5mg can reduce the length of hospital stay in patients with more severe pneumonia. So, apart from the different half-lives of prednisolone and dexamethasone, we should note that corticosteroids for mild and moderate pneumonia are not indicated. According to the results of RCTs clearer benefits of corticosteroids in patients with pneumonia were demonstrated using stress doses in the presence of cortical insufficiency, ARDS, and severe sepsis. These are the recommendations of the consensus guidelines for patients admitted to the ICU with severe CAP with either shock or acute lung injury [63]. It has been proposed [64] to diagnose cortical insufficiency in the presence of cortisol blood levels $\leq 10 \mu\text{g/dL}$ or increase in cortisol levels $\leq 9 \mu\text{g/dL}$ after cosyntropin stimulation test. The diagnosis

of cortical insufficiency is not always available and easy at bedside in daily practice, albeit it should be preferable before to administer steroids. A positive linear correlation has been shown between cortisol levels and the severity of the CAP, but corticosteroids may change this [65]. In addition, genetic information could help to identify patients for a more personalized treatment. Nevertheless, common practical criteria for severe pneumonia that could be taken in consideration by the clinician for glucocorticoid therapy are: $\text{PaO}_2:\text{FiO}_2 < 250$, respiratory rate > 30 bpm, bilateral infiltrates at chest-X-ray, and $> 3-4$ fold higher than normal CRP levels. When the decision to use corticosteroids is taken, the patient should be protected with anti-acid agents, and strictly monitored to early detect infections, hyperglycemia, hypokaliemia, and other possible adverse events. Steroids should be stopped in patients whose vasopressor dependency (dosage of norepinephrine or equivalent of greater than $0.1 \mu\text{g/kg}$ per minute) has not improved within 2-4 days of glucocorticoids [66].

Conclusions

The debate about the use of corticosteroids as adjunctive therapy for patients with pneumonia is far from being concluded. In spite of a great number of patients included in RCTs, further more robust data is needed regarding the optimal choice of the patients and glucocorticoids dose regimen. Nevertheless, from a clinical point of view, the amount of knowledge obtained from recent RCTs make it feasible to consider the use of stress doses

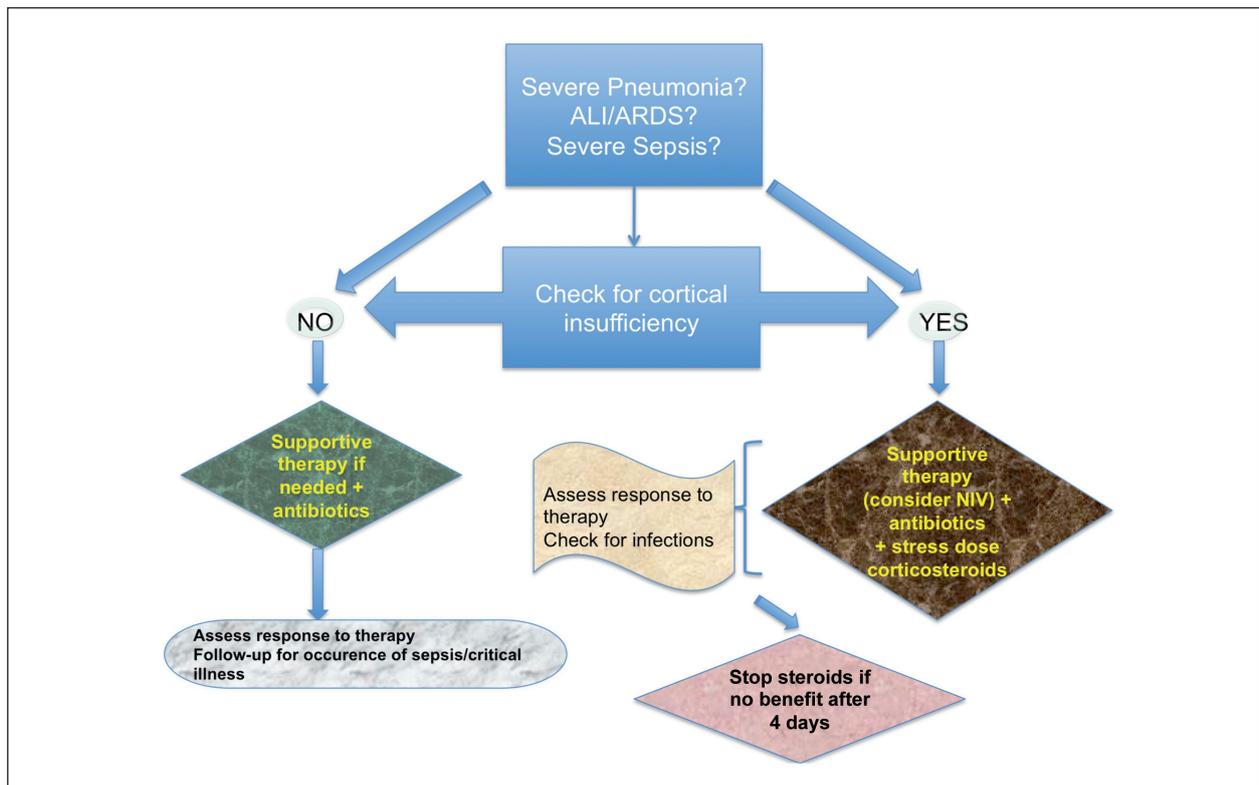


Fig. 1. - Decisional Flow-chart to consider the use of corticosteroids for pneumonia. NIV = Noninvasive ventilation.

of corticosteroids for pneumonia when a cortical insufficiency is diagnosed, or when Acute Lung Injury (ALI)/ARDS, severe sepsis, and/or severe pneumonia criteria are detectable (figure 1). The risk/benefit ratio of glucocorticoids should be always determined in each patient. A prolonged course (at least 7 to 10 days) of low-dose corticosteroids (e.g. Hydrocortisone 200 mg/day) may be helpful in patients with severe pneumonia within 12 hours of the onset of shock [64]. While the outcome benefit of prolonged low-dose glucocorticoids remains to be determined, such a strategy decreases vasopressor dependency and appears to be safe (no excess mortality, infections, myopathy). In fact, infection surveillance is critical in patients treated with corticosteroids, and to prevent the rebound phenomenon, the drug should be weaned slowly.

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