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Is Prolonged Low-Dose Glucocorticoid Treatment Beneficial in Community-Acquired Pneumonia?

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Abstract Community-acquired pneumonia (CAP) has a significant impact on public health in terms of short-term and long-term morbidity and mortality. Irrespective of microbiological etiology, the host's inability to fully downregulate systemic inflammation is the dominant pathogenetic process contributing to acute and long-term morbidity and mortality in CAP. Glucocorticoids are the natural regulators of inflammation, and their production increases during infection. There is consistent evidence that downregulation of systemic inflammation with prolonged low-dose glucocorticoid treatment in patients with severe sepsis and acute respiratory distress syndrome improves cardiovascular and pulmonary organ physiology. A recent meta-analysis of pooled controlled small trials (n = 970) of patients admitted with CAP found improved short-term mortality in the subgroup with severe CAP and/or receiving >5 days of glucocorticoid treatment. We have expanded on this meta-analysis by including patients with CAP recruited in trials investigating prolonged low-dose glucocorticoid treatment in septic shock and/or early acute respiratory distress syndrome (n = 1,206). Our findings confirm a survival advantage for severe CAP (RR 0.66, 95% confidence interval 0.51–0.84; p = .001). A large randomized trial is in progress to confirm the aggregate findings of these small trials and to evaluate the long-term effect of this low-cost treatment.

Keywords Community-acquired pneumonia · Glucocorticoids · Inflammation · Sepsis · ARDS · Cardiovascular disease

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Short- and Long-Term Impact of Community-Acquired Pneumonia on Morbidity, Mortality, and Health-Care Cost

Community-acquired pneumonia (CAP) is a common infection with a wide spectrum of clinical severity ranging from a self-limiting illness to life-threatening septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction. While mortality for pneumonia has decreased sharply following the introduction of antibiotics in the 1940s, since 1950, the overall acute (hospital) mortality has either remained stable or increased [1]. Acute mortality (≈4%–6% during initial hospitalization) makes pneumonia, with ≈55,000 deaths per year, the eighth most common cause of death in the U.S. [2]. Most hospital deaths, however, occur after eradication of bacteria from tracheal secretions and blood stream [3, 4], implying that adequate antibiotic treatment alone may be insufficient in achieving additional decline in morbidity and mortality. Survivors experience substantial and persistent new cognitive impairment and functional disability [5–12, 13••, 14–17]. This excess disability and mortality after the original hospitalization for pneumonia extends for years [15–21]. This new awareness calls for reexamining our approach to the treatment of pneumonia and for urgent research efforts proportional to the actual public health impact of the disease [18, 22].

Dysregulated Systemic Inflammation: A Biologic Rationale for the Use of Prolonged Low Doses of Corticosteroids in Patients with CAP

Systemic Inflammation and Pneumonia

There are two major components of an infection: pathogen (s) and the host inflammatory response. Pneumonia develops when pathogens invading the sterile lower respiratory tract activate the innate immune response to produce local and systemic inflammation [23, 24]. Even when the pulmonary inflammatory response is compartimentalized to the affected lung, patients admitted to the hospital with CAP or health-care-associated pneumonia (HCAP) have increased circulating levels of inflammatory and hemostasic markers (systemic inflammation) [17, 25••, 26, 27]. Irrespective of microbiological etiology, the host's inability to fully downregulate systemic inflammation (i.e., dysregulated systemic inflammation) is the dominant pathogenetic process contributing to acute and long-term morbidity and mortality in CAP.

Persistent, as opposed to short-lived, elevation of circulating inflammatory and hemostasic markers over time strongly correlates with worsened hospital and 1-year mortality, independently of demographic characteristics and comorbidities.

The Role of Glucorticoid During Insufficient Adrenal Response and as Regulator of Inflammation

An intact hypothalamic–pituitary–adrenal (HPA) axis with an effective intracellular glucocorticoid (GC)-mediated anti-inflammatory activity is indispensable for host survival during the stress response following exposure to an infectious agent. GCs are the most important physiologic inhibitors of inflammation [28] and affect thousands of genes involved in stress-related homeostasis [28, 29]. Both the physiological and pharmacological actions of GCs are mediated by the GC receptor (GR), a member of the nuclear receptor superfamily of ligand-dependent transcription factors. The GR enhances or represses transcription of target genes by binding specific elements of DNA and recruiting coactivators or corepressors that modulate the activity of RNA polymerase II by a unique means of cross-talk between nuclear and cell surface receptors [30]. Strong experimental and clinical evidence demonstrates that innate or treatment-induced reduction (downregulation) of systemic inflammation is necessary to decrease morbidity and improve survival in sepsis [31]. In patients with severe CAP and septic shock, a relatively insufficient adrenal response has been observed during infection, associated with a higher risk of death. The spectrum of this insufficient adrenal response has been shown in severe CAP, ALI/ARDS, severe sepsis, and whenever there is a GC tissue resistance together with an exaggerated and protracted proinflammatory response [32, 33]. The term *critical illness related corticosteroid insufficiency* (CIRCI) was recently proposed by an expert panel to describe the dysfunction of the HPA axis that occurs during the continuum of sepsis-associated systemic inflammation and other critical illnesses [34]. CIRCI can be defined as inadequate intracellular GC anti-inflammatory activity for the severity of the patient's illness. The mechanisms leading to impaired GR-mediated downregulation of inflammation are complex and partly understood. In the simplest terms, CIRCI can result either from insufficient availability of GCs to the cell or from intracellular resistance/insensivity to GCs (despite elevated circulating cortisol) [34]. These two conditions are affected to a significant extent by the intensity of systemic inflammation and are potentially reversible with quantitatively and temporally adequate prolonged GC administration [35, 36].

There is consistent evidence that prolonged low doses of GCs in patients with severe sepsis and ARDS, mostly caused by pneumonia [37], downregulate systemic inflammation and significantly improve cardiovascular and pulmonary organ physiology [34, 35, 38].

Duration of Glucocorticoid Treatment

Duration of GC treatment is an important determinant of both efficacy and toxicity [39]. Optimization of therapy with GCs is affected by two factors: (1) biological duration of the disease process (systemic inflammation and CIRCI) and (2) recovery time of the HPA axis after treatment is discontinued [40].

1. Longitudinal measurements of plasma cytokine levels in CAP have shown that after clinical resolution of pneumonia, inflammatory cytokines (tumor necrosis factor [TNF]-α and interleukin [IL]-6) and D-dimer remain elevated for weeks [25••, 26]. While the clinical signs for systemic inflammatory response syndrome (SIRS: fever, tachycardia, tachypnea) tend to resolve within 3 days of admission [41], TNF-α and IL-6 remain elevated for at least 22 days (limit of measurement) [25••]. These data, similar to those reported for patients with sepsis-induced ARDS (most of whom had CAP) [42], clearly demonstrate that biological resolution lags weeks behind clinical resolution.

2. Prolonged GC treatment is associated with downregulation of GR levels and suppression of the HPA axis, affecting systemic inflammation after treatment is discontinued. Experimental work has shown that short-term exposure of alveolar macrophages [43] or animals to dexamethasone is followed by enhanced inflammatory cytokine response to endotoxin [44]. Similarly, normal human subjects pretreated with hydrocortisone had significantly higher TNF-α and IL-6 response after endotoxin challenge, as compared with controls [45]. GC

treatment downregulates GR levels in most cell types, thereby decreasing the efficacy of the treatment. Downregulation occurs at both the transcriptional and traslational levels, and GC treatment decreases receptor half-life by approximately 50% [46]. In experimental animals, overexpression of GRs improves resistance to endotoxin-mediated septic shock, while GR blockade increases mortality [47]. Second, even after a few days of GC treatment, removal without tapering leads to adrenal suppression in 45% of patients, with gradual recovery over a period of 14 days [48]. The concept of *rebound* 24–36 h following removal of steroid treatment was initially reported by Wagner and collaborators in 1956 [49]. For decades, treatment-associated adrenal suppression has been part of standard teaching in medical schools; the product insert provided by the manufacturer (Pfizer) states that "drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage" [50].

Support for an association between longer duration of treatment and improved medium-term survival is provided by the *Pneumocystis jiroveci* pneumonia literature, where a 21-day treatment led to a sizable reduction in 3-month mortality (18% vs. 27%; $p = .02$) [51]. Another factor stressing the importance of duration of GC treatment is the actual biological duration of the disease process (systemic inflammation) that causes long-term morbidity and mortality [52].

The Long-Term Effects of Dysregulated Systemic Inflammation

An inflammatory and procoagulant load in patients who have pneumonia leads to excess morbidity and mortality both during hospitalization and after hospital discharge. The traditional pathophysiological model of pneumonia that equated the presence of SIRS with the duration of biologically significant systemic inflammation, which is damaging to the host, is incorrect. Biological resolution lags weeks behind clinical resolution; therefore, it is not a reliable indicator of disease activity. Pneumonia patients, admitted with or without severe sepsis, are discharged from the hospital with a clinically silent low-grade systemic inflammation and prothrombotic state that has a negative impact on mortality that is greater than one of acute (clinically apparent) systemic inflammation. The most robust contribution to this field originates from Kellum [25••] and Yende [16, 27], using the large GenIMS data set (1,886 CAP patients) that included daily measurements until day 7 and once weekly thereafter. Similar to inflammatory cytokynes, higher levels of D-dimer (hemostasis marker) at hospital admission correlated with worsened mortality in the hospital [43] and at 90 days [26]. Even after clinical resolution of pneumonia, inflammatory cytokynes (TNF-α and IL-6) and D-dimer remain elevated for weeks [25••, 26]. While the clinical signs for SIRS (fever, tachycardia, tachypnea) tend to resolve within 3 days of admission [42], TNF-α and IL-6 remain elevated for at least 22 days [25••]. IL-6 levels obtained at hospital discharge in clinically stable patients (>90% without SIRS criteria) strongly correlate with subsequent 1-year mortality after adjusting for age, race, gender, comorbidity score, and APACHE III [16]. The excess mortality in patients with low versus high IL-6 approximates the one reported by Kaplan et al. [7]. Similarly, higher levels of D-dimer at hospital discharge correlate with subsequent 1-year mortality and late cardiovascular events (myocardial infarction, stroke, and atherosclerotic heart disease) [27]. Table 1 shows the short- and long-term morbidity associated with acute and chronic systemic inflammation in patients with pneumonia. Particularly, a growing body of literature points to an association between systemic inflammation accompanying pneumonia and progression of underlying cardiovascular disease [45, 46]. Lowering this inflammatory load may improve short- (hospitalization) and long-term (post hospitalization) outcome. Unfortunately, all published randomized trials on GC in pneumonia and sepsis were designed without awareness of these fundamental concepts, so treatment of sepsis omitted being directed to dysregulated chronic inflammation and continued until disease resolution.

Steroids for CAP: Evidence from the Literature

As early as 1956, favorable clinical effects of hydrocortisone (80 mg per day orally tapered over 5 days) were reported in patients with pneumococcal pneumonia [49]. However, after the introduction of antibiotics, research interest faded until recently. The use of GC treatment in order to modulate inflammation in patients with CAP was targeted in experimental studies and a few randomized clinical trials, but the results were not univocal. Moreover, in spite of a pathophysiologic rationale [53] for GC use in CAP only for a prolonged low dose (stress dose), most studies did not use this dose regimen.

Prolonged Low Dose of Glucocorticoids Covering 24 h/Day

It is noticeable that only three recent randomized clinical trials (RCTs) [54•, 55, 56] were performed using a 24-h GC coverage with a prolonged low dose of GCs for at least 7 days in patients with CAP (Table 2). The other RCTs [57–62] used corticosteroids for a shorter number of days with or without a dose regimen covering 24 h/day (Table 3). It has been reported [63] that a longer duration of GC treatment covering 24 h/day may prevent rebound systemic inflammation and clinical deterioration due to abrupt discontinuation of GC treatment [64]. Not surprisingly, all the RCTs using a prolonged low dose of corticosteroids were able to reach the study end points. Otherwise, in the other

Table 1 Short- and long-term morbidity associated with acute and chronic systemic inflammation in patients with CAP

	Short-term (Acute)	Long-term (Chronic)
System	Morbidity associated with acute severe systemic inflammation	Morbidity associated with chronic, low-grade systemic inflammation
Cardiovascular	Septic shock/vasopressor dependency	Progression of ASCVD[a]
	Myocardial injury/dysfunction Atrial and ventricular arrhythmias	Sudden cardiac death
	Sudden cardiac death	
Pulmonary	Acute respiratory failure (pneumonia) Acute respiratory distress syndrome	Weaning failure/ventilator dependency
Neurological	Delirium	Long-term cognitive impairment
	Neuromuscular dysfunction	Post traumatic stress disorder
	Stroke	Depression
	Autonomic dysfunction	Muscular weakness
Renal	Acute kidney injury	Unknown
Hematologic	Consumption of platelets and clotting factors	Low grade procoagulant state
Infections	Delayed resolution of pneumonia	Increased rate of infections
	Increased rate of nosocomial infections	Hospitalization for recurrent pneumonia
HPA axis[b]	CIRCI[c]	Impaired adrenal response to stress
Other endocrine/ metabolic dysfunction	Vasopressin deficiency Insulin resistance/hyperglycemia	Unknown
	Growth hormone deficiency	
Lipid metabolism	Reduction in total cholesterol, HDL cholesterol, and apolipoprotein A1 and B	HDL cholesterol continues to increase toward baseline level over 6 months [46]
Multisystem	Multiple organ dysfunction	Impaired functional status
	Increased post-ICU discharge mortality	Impaired quality of life
		Increased long-term mortality

[a] *ASCVD* atherosclerotic cardiovascular diseases

[b] *HPA axis* hypothalamic–pituitary–adrenal axis

[c] *CIRCI* critical illness-related corticosteroid insufficiency

group of RCTs, only the study by Meijvis [62], using a long-lasting corticosteroids (dexamethasone) for 4 days, got the primary end point reducing the length of hospitalization in comparison with placebo.

Experimental Literature

Two recent experimental studies [65, 66] have demonstrated that treatment with GCs, in comparison with no treatment, was associated with a significant reduction in circulating and pulmonary inflammatory cytokine levels [65, 66], an improvement in histopathological severity scores [65, 66], and a decreased pulmonary bacterial burden [65]. A large experimental study of *Escherichia coli* pneumonia in mice found that GC treatment effectively reduced the risk of death following challenge with low or high numbers of organisms [28].

Clinical Trials of Glucocorticoids for CAP

In the last 10 years, randomized controlled trials have investigated the effects of prolonged GC treatment in each phase of the temporal continuum of pneumonia-associated systemic inflammation: severe sepsis, septic shock, and ARDS. In these clinical trials, the protocol design varied widely for treatment (type of GC, daily dosage, duration of treatment, and tapering), patient selection, and study end points. Table 4 shows GC trials in patients with pneumonia-associated sepsis, severe sepsis, and ARDS [54•, 55–63, 67, 68]. Recent meta-analyses provided evidence of improvement in patient-centered outcomes for patients with septic shock [29] or ARDS, with most cases attributable to pneumonia [69, 70]. A limited number of trials have investigated GC treatment in patients with nonsevere [49, 56, 59–62] and severe [54•, 55, 58, 63, 69–71] pneumonia. Prospective, randomized clinical studies have also been undertaken, as follows.

1. *Severe pneumonia requiring ICU admission*. Preliminary small trials investigating steroid treatment for at least 7 days duration [54•, 55] and subgroup analysis of trials in patients with severe sepsis [63], septic shock [67, 71], or ARDS [68] show weak evidence for a mortality benefit in patients with severe pneumonia requiring ICU

Table 2 Randomized controlled trials (RCTs) of prolonged low-dose glucocorticoids for patients with CAP (24h/day corticosteroid coverage, and at least 7 days treatment)

1st Author, year	No. pazients, Primary outcome	CS dose regimen	Severity of pneumonia	Results	Primary end point reached?	Study limitations
Confalonieri, 2005	56, PaO_2:FiO_2 improvement	200 mg HC bolus, then 240 mg/day HC for 7 days	Severe pneumonia (ATS 1991), most of them with sepsis	Earlier PaO_2:FiO_2 improvement with GC , improved survival with GC in hospital and at 2 months	Yes	Early interruption for more deaths in the placebo arm, small sample size
Sabry, 2011	80, PaO2:FIO2 >300 or >100 than study entry, and reduced septic shock	Loading dose 200 mg HC over 30 min, followed by 300 mg/day for 7 days	Intubated ICU patients with severe pneumonia	GC significantly improved PaO2:FIO2 and SOFA score at day 7	Yes	Small sample size, NIV was not used for weaning
Fernandez-Serrano, 2011	56, requirement for MV and PaO_2:FiO_2 improvement	Bolus IV 200 mg 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	GC reduced need for MV (not significant) and improved PaO_2:FiO_2 significantly earlier than placebo	Yes	Small sample size

ALI acute lung injury; *GC* glucocorticoids; *HC* hydrocortisone; *NIV* noninvasive ventilation; *MV* mechanical ventilation; *MP* methylprednisolone

Table 3 Randomized controlled trials (RCTs) of glucocorticoids for patients with CAP (short-term treatment with or without 24 h/day glucocorticoid coverage)

First author, year	No. patients, Primary outcome	Glucocorticoid dose regimen	Severity of pneumonia	Results	Primary end point reached?	Study limitations
van Woensel, 2003	85, duration of MV	IV DEX 0.15 mg/kg 6-hourly for 48 h	Mild pneumonia, bronchiolitis	GC Increased LOS, need for MV increased	No	Several drop-outs or losses to follow-up
Marik, 1993	30, mortality, ICU LOS, and serum TNF-α level	10 mg/kg of hydrocortisone or placebo IV 30 min prior to starting antibiotic therapy	Severe pneumonia	GC reduced LOS and duration of MV	No	Very short duration interventional therapy with CS (possible rebound)
McHardy,1972	126, time to clinical resolution	20mg/day P	Mild	No difference between groups	No	Small sample size, bias in study design
Mikami, 2007	31, days to normalization of SpO_2	40 mg/d P IV for 3 days	Moderate and severe pneumonia	GC did not cause faster SpO_2 normalization, but shortened antibiotic duration	No	Small sample size, open label study design
Snijders, 2010	213, clinical cure at day 7	40 mg P IV for 7 days	Mild-to-severe hospitalized patients	Primary end point not reached	No	Mainly mild pneumonia, possibility to receive CS also for controls
Meijvis, 2011	304, LOS	IV DEX (5 mg once a day) for 4 days	Mild-to-severe (PSI I–V)	LOS reduction with CS	Yes	Possible use of CS in case of sepsis with bias analysis , CS effects not evaluated if need for MV

GC glucocorticoids; *P* prednisone; *MP* methylprednisolone; *HC* hydrocortisone; *DEX* desamethasone; *LOS* length of hospital stay; *MV* mechanical ventilation; *SpO_2* pulse oxymetry; *TNF* tumor necrosis factor

Table 4 Glucocorticoid trials in pneumonia associated with sepsis, severe sepsis, and ARDS

Pneumonia severity	No.	Treatment type and dosage	Days	Primary outcome
Sepsis ($N = 843$)				
Wagner, 1956	113	Hydrocortisone, 560 mg over 5 days	5	Hospital mortality
McHardy, 1972	126	Prednisolone, 20 mg	7	Hospital mortality
Mikami, 2007	31	Prednisolone 40 mg	3	Length hospital stay
Snijders, 2010	213	Prednisolone 40 mg	7	Day 7 clinical cure
Fernandez, 2011	56	Methylprednisolone (day), (1) 200 mg, (2–4) 20 mg Q 6 h, (5–7) 20 mg Q 12 h, (8–10) 20 mg/d	10	Need for mechanical ventilation
Meijvis, 2011	304	Dexamethasone 5 mg/day	4	Length hospital stay
Severe sepsis ($N = 181$)				
Marik, 1993	30	Hydrocortisone, 10 mg/kg – 1 dose	1	ICU mortality
Confalonieri, 2005	46	Hydrocortisone infusion 10 mg/h	7	Day 8 PaO2:FiO2
Nawab, 2011	25	Hydrocortisone infusion 10 mg/h	7	Day 7 MODS
Sabry, 2011	80	Hydrocortisone infusion 12.5 mg/h	7	Day 8 PaO2:FiO2 MODS
Septic shock ($N = 211$)				
Annane, 2002	101	Hydrocortisone 50 mg Q 6 h and Fludrocortisone 50 g/d	7	Day 28 mortality
Corticus, 2008	110	Hydrocortisone (day), (1–5) 50 mg Q 6 h, (6–8) 50 mg Q 12 h, (9–11) 50 mg Q 24 h	11	Day 28 mortality
ARDS ($N = 25$)				
Meduri, 2007	25	Methylprednisolone 1 mg/Kg/d	25	Day 7 lung injury score

MODS multiple organ dysfunction

admission (CAP/HCAP subgroup with high mortality). The two RCTs that investigated corticosteroid treatment exclusively in patients with pneumonia [54•, 55] consistently reported by day 8 a significant reduction in C-reactive protein level, duration of mechanical ventilation, organ dysfunction score, chest radiograph score, and development of septic shock. The most beneficial effect was in those patients on mechanical ventilation, both invasive and noninvasive. One of our trials [54•] found a reduction in mortality. A large Cooperative Study Program randomized trial (CSP #574 ESCAPe) is in progress to study the effect of prolonged treatment (20 days) with methylprednisolone in patients on mechanical ventilation (CSP #574 ESCAPe, ClinicalTrials.gov Identifier: NCT01283009).

2. *Nonsevere pneumonia*. The literature for patients with nonsevere pneumonia includes six trials ($n = 829$; range,

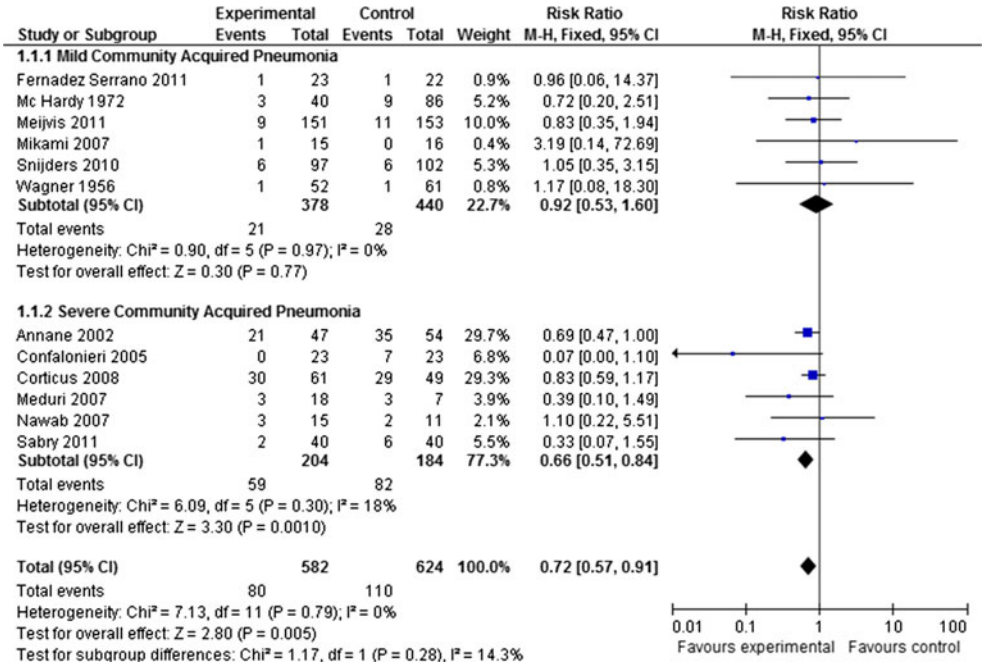

Fig. 1 Updated meta-analysis of controlled studies on glucocorticoids for CAP: comparison of severity subgroups

56–304) conducted over a span of 54 years [49, 56, 59–62]. Three trials [56, 61, 62] were published over the last 15 months, underlying the intense interest in this field. These studies included patients with low acute mortality risk (6%) and were insufficiently powered to demonstrate a short-term mortality benefit. The largest trial [62] reported a significant reduction in duration of hospitalization (primary end point: 6.5 vs. 7.5 days; $p < .05$) and improved social functioning by day 30 ($p < .01$) without increased rate of adverse events. All but one trial [61] reported faster clinical resolution [49, 56, 59, 62]. No study addressed the effects of GC treatment on long-term morbidity and mortality.

Meta-Analysis of Glucorticoid Treatment for CAP

A meta-analysis by Nie et al. was published in 2012 [72] that included both randomized and quasirandomized trials of corticosteroid treatment in adult patients with CAP of mixed severity. The durations of different corticosteroid treatment ranged from 1 to 9 days. Effects on primary outcome (mortality) and secondary outcomes (adverse events) were accessed in this meta-analysis. Nine trials involving 1,001 patients were included [54•, 55–62]. Use of corticosteroids did not significantly reduce mortality when all studies were included (Peto odds ratio [OR] 0.62, 95% confidence interval [CI] 0.37–1.04; $p = .07$). In a subgroup analysis categorizing patients by severity, a survival benefit was found among severe CAP patients (Peto OR 0.26, 95% CI 0.11–0.64; $p = .003$). Importantly, a subgroup analysis by duration of corticosteroid treatment, significantly reduced mortality among patients with prolonged (>5 days) corticosteroid treatment (Peto OR 0.51, 95% CI 0.26–0.97; $p = .04$; I2 = 37%). Corticosteroids increased the risk of hyperglycemia (Peto OR 2.64, 95% CI 1.68–4.15; $p = .0001$), but without increasing the risk of gastroduodenal bleeding (Peto OR 1.67, 95% CI 0.41–6.80; $p = .47$) and superinfection (Peto OR 1.36, 95% CI 0.65–2.84; $p = .41$) [72]. We have performed a new meta-analysis (Fig. 1) based on the expanded literature shown in Table 4. This new analysis provides additional evidence for a significant short-term survival benefit in patients with severe CAP ($p = .001$). Figure 1 shows the Forrest plot of survival in patients with nonsevere CAP versus severe CAP.

Conclusions

The two major components of pneumonia are pathogen(s) and inflammation. Following the reduction in mortality associated with the introduction of antibiotics, morbidity and mortality for pneumonia has remained unchanged or increased. The greatest shift in our understanding of the true impact of pneumonia on the host has been the documentation of substantial continuing excess mortality for more than 2 years after surviving an episode of CAP. It is now appreciated that the degree of pneumonia-associated systemic inflammation at hospital presentation and at hospital discharge significantly contributes to acute and long-term morbidity and mortality more than do demographics and comorbidities [52]. For the foreseeable future, GCs will remain the most viable candidate for first-line treatment, thanks to their rapid and profound anti-inflammatory effect, safety profile, and low cost. The immunoregulatory effect of GCs given at a prolonged low-dose regimen is able to downregulate proinflammatory cytokyne production and to improve organ function. Nevertheless, the literature of GC treatment for pneumonia had controversial results due to different patient selection criteria, GC dose regimens, and study end points. However, only RCTs using a dose regimen of corticosteroids covering 24 h/day reached the study end points. A recent meta-analysis [72] of pooled controlled small trials showed improvement in acute mortality in patients with severe CAP, but not with CAP without severe sepsis [73]. We have expanded on this meta-analysis by including patients with CAP recruited in trials investigating prolonged low-dose GC treatment in septic shock and/or early acute respiratory distress syndrome. Our findings confirm a survival advantage for severe CAP. A large randomized trial is in progress to confirm the aggregate findings of these small trials and to evaluate the long-term effect of this low-cost treatment.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- • Of importance
- •• Of major importance

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