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Hydrocortisone in septic shock, ARDS and severe pneumonia

Hydrokortison im septischen Schock, bei ARDS und schwerer Pneumonie

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► **Zusammenfassung** Hydrokortison konnte die Mortalität und die Dauer des septischen Schocks senken. Neuere Untersuchungen weisen auf einen Benefit der sogenannten Substitutionstherapie bei schwerer Pneumonie und Sepsis hin, während beim ARDS die Studien geteilte Resultate aufweisen. Der Mechanismus für die durch Hydrokortison bedingten Verbesserungen ist nicht erklärt, aber eine bessere Vasopressoren-Antwort und die Beeinflussung einer überschießenden Immunreaktion scheinen von Bedeutung zu sein. Die Patienten mit Nebenniereninsuffizienz scheinen desweiteren am meisten von einer solchen Hydrokortisontherapie zu profitieren. Das Screening einer solchen Dysfunktion sollte bei jedem Intensivpatienten mit schwerer Erkrankung erfolgen.

► **Schlüsselwörter** ARDS – Sepsis – septischer Schock –

Hydrokortison – Pneumonie – Nebenniereninsuffizienz

► **Summary** Hydrocortisone has decreased shock duration and improved outcome in patients with septic shock. More recent trials have suggested a positive effect of this so-called replacement therapy in severe pneumonia and sepsis. The results of hydrocortisone during ARDS are equivocal. The mechanism responsible for the hydrocortisone-induced benefit remains uncertain, but improved vasopressor response and the restrain of exaggerated systemic inflammation may be important. Adrenal insufficient screening should be performed in every ICU patient with severe disease.

► **Key words** ARDS – sepsis – septic-shock – Hydrocortisone – Pneumonia – adrenal insufficiency

Introduction

Ever since the discovery of the hypothalamic-pituitary-adrenal axis and the consequences of its dysfunction by Thomas Addison in 1855, the corticoid replacement therapy has remained controversial [1]. This is especially true for its use in the ICU where corticosteroids were used in ARDS, sepsis and septic shock. During the 1980's high dose corticosteroid

therapy (6–8 g/d) for a short time (4–24 h) was used to treat those life-threatening conditions with the aim of suppressing an exacerbated inflammatory response [2, 3]. However soon its efficacy was questioned as several clinical studies demonstrated no benefit so that the strategy was dismissed [4]. In the late 1990's as well as at the beginning of the new millennium, a more profound understanding of the pathophysiology of adrenal insufficiency led to a revival of the replacement strategy.

The adrenal gland and glucocorticoids

The human adrenal gland, weighing about 4–6 g, is subdivided into two functional units: the medulla and the cortex. The adrenal cortex is partitioned into three concentric zones of steroid-synthesizing cells: the glomerulosa producing the mineralocorticoids (aldosterone), the reticularis secreting the androgens (dihydroepiandrosterone, Δ^4 -androstenedione) while the production of the glucocorticoids (cortisol) lies in the fasciculata. The adrenal medulla produces sympathetic hormones such as epinephrine or norepinephrine.

The basic compound necessary for the production of steroids is cholesterol. Cholesterol is captured from the low density lipoproteins (LDL) and transformed by numerous enzymes such as cytochromes and 3β -hydroxysteroid dehydrogenase.

Cortisol is transported in the blood in three forms: free cortisol, cortisol bound to the proteins as well as cortisol metabolites. Free cortisol, which is only found in small quantities in the plasma (5–10%), represents the active form. The two main binding proteins are the cortisol-binding protein (CBG) and albumin. Cortisol is metabolized in the liver where it is inactivated by 11β -hydroxysteroid dehydrogenase. The half-life of cortisol is 60–70 min, while it is 180 min for hydrocortisone and methylprednisolone.

The secretion of cortisol is tightly regulated by two major glands: the hypothalamus exerts its action on the pituitary gland by secreting cortisol releasing hormone (CRH) while the pituitary gland itself stimulates the adrenal gland by releasing adrenocorticotrophic hormone (ACTH) (Fig. 1). The cortisol plasma concentration follows a diurnal rhythm with its peak concentration between 7 and 8 am each day and a nadir about midnight. This diurnal cycle is lost in case of an aggression like an infection.

Molecular actions and consequences on the inflammatory response of glucocorticoids

Because of its lipophilic nature, cortisol enters the cell passively through its membrane. It then binds to the glucocorticoid receptor α (GR α) which, in the absence of cortisol, forms an inactive heterodimer with several heat-shock proteins (HSP). In the presence of cortisol, GR α is dissociated from the HSP so that it is able to enter the cellular nucleus through the nuclear pores. As a dimer, it binds then to the glucocorticoid receptor elements (GRE) and modulates the transcription of numerous genes, inducing the production or suppression of numerous proteins

Fig. 1 The hypothalamic-pituitary-adrenal axis and its aggressors (CRH corticotropin-releasing hormone, ACTH adrenocorticotrophic hormone)

involved in the inflammatory process. Most importantly, glucocorticoids exert their anti-inflammatory action by suppressing the production of the pro-inflammatory cytokine NF- κ B. This suppresses the production of almost all pro-inflammatory cytokines such as tumor necrosis factor α (TNF- α), interferon- γ (IFN- γ) and several interleukins (IL-1, IL-2, IL-3 IL-6, IL-12) (Fig. 2).

As a result, glucocorticoids block the apoptosis of neutrophils while promoting cell death from eosinophils and basophils. Furthermore, glucocorticoids enhance the clearance of foreign antigens and inhibit their presentation by blocking the maturation of dendritic cells. By blocking the production of IL-12, glucocorticoids slow the development of the Th1-directed cellular immune response while promoting the Th2-directed humoral response by enhancing the IL-10 secretion. In short, glucocorticoids restrain systemic inflammation preventing an overreaction of the immune system to foreign antigens. Unfortunately by doing so, they also increase the probability of opportunistic infections [5, 6].

Origin of the adrenal insufficiency

Pituitary insufficiency is a common condition in the critically ill. Of all patients admitted to the ICU, 30% have an altered hypothalamic-pituitary-adrenal axis, in the septic shock group the incidence even exceeds 60% [7–9]. There are multiple reasons for this insufficiency (Table 1).

Fig. 2 The glucocorticoid signaling pathway (*GR α* Glucocorticoid receptor α , *GRE* glucocorticoid responsive element, *HSPs* heat shock proteins)

Table 1 Origin of the adrenal insufficiency

Primary adrenal insufficiency	Tuberculosis Systemic fungal infection Auto-immune adrenalitis HIV infection Antiphospholipid syndrome Metastatic carcinoma (Lungs +++) Acute hemorrhage (Meningococemia, Disseminated intravascular coagulation)
Secondary adrenal insufficiency	Head trauma Pituitary or metastatic tumor Pituitary surgery or radiation
Drugs inducing adrenal insufficiency	Glucocorticoid treatment (systemic or topical) Anticoagulants Aminoglutethimide Mitotane Ketoconazole Fluconazole Etomidate Dexmedetomidine Phenobarbital Phenytoin Rifampicine Medroxyprogesterone Anti-depressant drugs Opiate drugs

The adrenal gland itself may be destroyed resulting in a primary adrenal insufficiency. Tuberculosis was the leading cause of acute and chronic adrenal insufficiency until the discovery of modern antibiotics. Later in the 1980's, the emergence of immunosuppression and immunosuppressive diseases as found, i.e., in HIV, AIDS or transplanted patients,

became the most frequent cause of primary adrenal insufficiency. Indeed, human cytomegalovirus has been found in the adrenal gland in 88% of patients who died of AIDS. *Cryptococcus neoformans*, *Toxoplasma gondii*, *Histoplasma capsulatum* infection are also responsible of the destruction of the supra-renal glandular tissue [10]. Numerous drugs used in the immunosuppressed patient impair adrenal function (notably ketoconazole, fluconazole or rifampin) [11–13]. Other drugs commonly used in the ICU are responsible for either a transitory or prolonged adrenal insufficiency. Most importantly, etomidate impacts steroidogenesis by blocking the adrenal mitochondrial hydroxylase resulting in a primary adrenal insufficiency. As a consequence, the use of this imidazole as an induction agent should possibly be avoided in patients with a septic condition [14, 15]. Another cause of primary adrenal insufficiency is an acute hemorrhage of the adrenal tissue as found in disseminated intravascular coagulation, meningococemia, or anticoagulation.

On the other hand, the destruction of the pituitary gland or the hypothalamus leads to secondary adrenal insufficiency. The most common condition responsible for this is sepsis and SIRS. The mechanisms are not fully understood yet, but it appears that numerous circulating pro-inflammatory factors such as $\text{TNF-}\alpha$ or neutrophil-derived corticostatsins inhibit the ACTH release of the pituitary gland [16].

Glucocorticoids such as prednisolone, methylprednisolone or dexamethasone may also induce secondary adrenal insufficiency by suppressing ACTH production. The degree of suppression depends largely on the time of steroid administration, but there is a

nonpredictable individual susceptibility as well [17]. Glucocorticoids do not affect the HPA axis when taken for less than 5 days. A treatment duration of 5–30 days induces an adrenal insufficiency which is reversible within 14 days. When glucocorticoids are taken for more than 30 consecutive days, the HPA recovery may last as long as 1 year [18, 19]. It is important to note that even inhaled glucocorticoids as used in asthmatics or in COPD patients may induce a HPA insufficiency to a varying degree [20, 21].

A peripheral glucocorticoid resistance may also be responsible for a relative adrenal insufficiency. In critical illness, glucocorticoid delivery can be decreased by a low serum glucocorticoid binding globulin (CBG) concentration and activity [22, 23]. The cleavage of CBG at the inflammatory site might be altered by a reduced neutrophil elastase. Furthermore, an increased activity of the 11- β hydroxysteroid dehydrogenase (HSD) induced by several cytokines (IL-2, IL-4, IL-12) enhances the conversion of the active cortisol to the inactive cortisone. As a consequence the cortisol concentration at the inflammatory site is reduced resulting in a relative adrenal insufficiency with significantly increased serum cortisol levels (≥ 34 g/dl).

Diagnosis of adrenal insufficiency

The diagnosis of an HPA failure is based on the serum cortisol level. As the critical ill patient loses his diurnal variation of the cortisol secretion, a specific timing for the cortisol blood level is not necessary and can be done at any time during the day [24]. The minimal level which is considered sufficient for a major stress has been much discussed as the proposed cortisol level ranges from 10 to 34 $\mu\text{g/dl}$. Several studies have established a threshold level of 19 $\mu\text{g/dl}$ as indicator for adrenal insufficiency [25–27]. When serum cortisol levels peak above 19 $\mu\text{g/dl}$, an adrenal stimulation test should be done. An increment (Δmax) of less than 9 $\mu\text{g/dl}$ indicates adrenal insufficiency while a plasma cortisol level over 34 $\mu\text{g/dl}$ suggests a tissue resistance to glucocorticoids (Fig. 3) [27].

The gold standard for adrenal stimulation remains the insulin-induced hypoglycemia test. Most experts agree that due to the contraindication of this test in critically ill patients, the “short synacthen stimulation test” with 250 μg of ACTH (SST) is the most useful diagnostic tool [27, 28]. The low dose short synacthen stimulation test with 1 μg of ACTH

Fig. 3 Detection and treatment strategy during sepsis and septic shock

(LDSST) may have better sensitivity. However, in the absence of major supportive trials, validation is still required.

It is important to note that the sensitivity and specificity of the ACTH stimulation tests is not good enough to detect all HPA failures by the scheme described above. Another issue which needs to be considered is the bypassing of the CNS-hypothalamo-pituitary axis which is not assessed by the SST or LDSST. An additional corticotropin releasing hormone (CRH) test was proposed by some authors. This has not yet been evaluated in critically ill patients and should not be used in current practice [29]. Hence clinical judgment remains one of the most important issues for deciding which patient needs replacement therapy [30].

Outcome of adrenal insufficiency

Based on the criteria above, the outcome of patients in septic shock has been evaluated. Indeed, basal cortisol levels as well as the cortisol response to stimulation by 250 µg synthetic ACTH (short synacthen test or SST) have been established as independent predictors of 28-day mortality. The classification into one of three groups based on cortisol levels has been proposed. The group with the worst outcome had a basal cortisol level <34 µg/dl and were non-responders to the SST (28-day mortality=82%). Basal cortisol levels >34 µg/dl and a response >9 µg/dl to the SST was linked to the best outcome (28-day mortality=26%) [31]. Based on those findings, numerous clinical trials have been set up to determine the efficiency of an adrenal substitution therapy in critical illness.

Treatment with low dose glucocorticoids in septic shock

Based on the results of the study above, Annane et al. assessed low dose glucocorticoid replacement therapy in septic shock in a randomized, double-blind, placebo-controlled trial including 300 patients. Hydrocortisone was given intravenously on a daily basis every 6 h as a 50 mg bolus. Moreover, a concomitant mineralocorticoid replacement therapy with a daily oral dose of 50 µg of 9α-fludrocortisone was administered. The treatment was introduced at the beginning of the septic shock and continued for 7 days. Eligible patients underwent a SST at the beginning of the replacement strategy subdividing the study population into responders (23%) and non-responders (77%) to the SST.

In the non-responder group, the 28-day mortality was reduced significantly: 73 deaths (62%) were documented in the placebo-group, while there were 60 deaths (53%) in the hydrocortisone group. The duration of shock was reduced and vasopressors were withdrawn within 28 days in 40% of the placebo group and in 57% in the treatment group.

These results were not found in the responder group, where mortality and shock duration were similar in the treated and the placebo group. Hence there is no benefit of hydrocortisone treatment in patients with an intact HPA axis [32]. It is important to note that there were no significant differences in adverse effects between the two groups. Indeed, low dose hydrocortisone treatment did not induce superinfections, gastrointestinal bleedings or psychiatric disorders and can be considered as relatively safe.

Oppert et al. investigated the effect of low dose hydrocortisone on the reversal of septic shock in a randomized, double-blind, placebo-controlled trial including 41 patients. Hydrocortisone was administered initially as a 50 mg bolus followed by a continuous infusion of 0.18 mg/kg. After cessation of vasopressors, hydrocortisone was reduced to 0.06 mg/kg during 24 h then further tapered by 0.02 mg/kg every day. After randomization, the patients underwent a SST and were divided into responders and nonresponders to the synthetic ACTH. A significant reduction in the time to vasopressor withdrawal was noted. Indeed, the mean vasopressor administration time was 53 h for the hydrocortisone group, while it was 120 h for the placebo group. Once again, the nonresponders to the SST had a larger benefit of the replacement therapy. Mortality however was not affected by the hydrocortisone treatment nor was the complication rate. Furthermore, Oppert analyzed different plasma cytokine levels during the treatment period. The pro-inflammatory cytokine interleukin-6 (IL-6), the anti-inflammatory Interleukine-10 (IL-10), the ex vivo LPS-stimulated IL-6 production as well as the ex vivo LPS-stimulated IL-1 production were initially highly elevated but declined under the sepsis therapy. The decline in the interleukine levels were significantly faster in the hydrocortisone group than in the placebo group [33]. Other recent studies testing hydrocortisone in septic shock also showed a benefit in terms of duration of vasopressor therapy and mortality [33–37] (Table 2).

Hydrocortisone and methylprednisolone in ARDS

More recently, Annane et al. performed a *post hoc* analysis of the efficacy of low dose hydrocortisone in septic shock patients with or without early acute

Table 2 Major randomized, double-blind, placebo-controlled trials assessing the effect of glucocorticoids in septic shock, ARDS, and severe pneumonia

Trial	Method	Treatment	Outcome
<i>Bollaert, 1998 (France)</i>	41 adults Septic shock 2 centers	Hydrocortisone 100 mg IV bolus every 8 h for 5 d then tapered over 6 d	Shock duration reduction: 4 d (HC) vs 13 d (P) Shock patients at d5: -47% (HC) D28 mortality: -31% (HC)
<i>Meduri, 1998 (US)</i>	24 adults Late ARDS 1 center	Methylprednisolone 2 mg/kg/d for 14 d then tapered over 24 d	Successful extubation at d10: 7 (MP) vs 0 (P) ICU mortality: 0% (MP) vs 63% (P) Hospital mortality: 13% (MP) vs 63% (P)
<i>Briegleb, 1999 (Germany)</i>	40 adults Septic shock 1 center	Hydrocortisone 100 mg 30 min IV infusion + 0.18 mg/kg/h continuous infusion until shock reversal then tapered off	Shock duration reduction: 2 d (HC) vs 7 d (P) Reduction of MODS No d28 mortality reduction
<i>Chawla, 1999 (USA)</i>	44 adults Septic shock 1 center	Hydrocortisone 100 mg IV bolus every 8 h for 5 d then tapered over 4 d	Shock duration reduction: 3 d (HC) vs 5 d (P) Shock patients at d3: -37% (HC) D28 mortality: -30% (HC)
<i>Yildiz, 2002 (Turkey)</i>	40 adults Sepsis (14), Severe sepsis (17), Septic shock (9) 1 center	Prednisolone 5 mg IV at 6:00 and 2.5 mg IV at 18:00 pm for 10 d or placebo	D28 mortality: -20% (Prednisolone)
<i>Anname, 2002 (France)</i>	300 adults Septic shock 19 centers	Hydrocortisone 50 mg IV bolus every 6 h + Fludrocortisone 50 µg/d orally for 7 d	Shock duration reduction: 7 d (HC) vs 10 d (P) Shock patients at d3: -20% (HC) D28 mortality: -10% (HC)
<i>Keh, 2003 (Germany)</i>	40 adults Septic shock 1 center	Hydrocortisone 100 mg 30 min IV infusion + 0.18 mg/kg/h continuous infusion for 3 d	Shock patients at d3: -40% (HC)
<i>Confalonieri, 2004 (Italy)</i>	46 adults Severe community acquired pneumonia 6 centers	Hydrocortisone 200 mg IV bolus then 10 mg/h for 7 d	Delayed septic shock: 0 (HC) vs 9 (P) ARDS reduction at d7: -48% (HC) Hospital mortality: -30% (HC) D60 mortality: -38% (HC)
<i>Oppert, 2005 (Germany)</i>	41 adults Septic shock 1 center	Hydrocortisone 100 mg 30 min IV infusion + 0.18 mg/kg/h continuous infusion until shock reversal then tapered off	Shock duration reduction: 53 h (HC) vs 120 h (P) No d28 mortality reduction
<i>Anname, 2006 (France)</i>	Post hoc analysis 300 adults Septic shock with ARDS and nonresponders to SST 19 centers	Hydrocortisone 50 mg IV bolus every 6 h + Fludrocortisone 50 µg/d orally for 7 d	Median time to death: 8 d (P) vs 17.5 d (HC) D28 mortality: -22% (HC) No differences in septic shock without ARDS between HC and P group No differences in responders between HC and P group

HC Hydrocortisone group, MP Methylprednisolone Group, P Placebo group, SST Short Synacthen Stimulation Test

respiratory distress syndrome (ARDS) using the data from their trial cited above [32]. The patients were separated into four groups according to their disease (septic shock patients with or without ARDS) and their SST results (responders or nonresponders). In the septic shock group with ARDS, the outcome in the nonresponder group was dependant on the treatment assigned. Indeed, the mean time to death was 8 days in the placebo group and 17 days in the hydrocortisone group. Days alive and off the ventilator were 2.6 ± 6.6 among nonresponders treated by placebo versus 5.7 ± 8.6 for the treatment group. The increase in P_aO_2/F_iO_2 was higher in the treated nonresponder group and the mortality was significantly reduced in the treatment group. 75% of the placebo

patients versus 53% of the treated patients died within 28 days.

Among responders to the SST no significant difference between treated groups and placebo groups was observed. In the septic shock group without ARDS the treatment with hydrocortisone did not show any benefit. Once again, no adverse events due to hydrocortisone were noted.

This *post hoc* analysis shows a clear benefit of hydrocortisone treatment in septic shock patients with ARDS who are nonresponders to the SST. It is important to note that the inefficiency of the hydrocortisone treatment in septic shock without ARDS should not lead to the conclusion that the benefit is due to a better treatment of ARDS. Indeed, the ret-

rospective character of this work and the small study population does not allow such conclusion [38].

Interestingly, those findings keep in touch with the studies using methylprednisolone in late ARDS [39–41]. In a randomized, placebo-controlled trial, Meduri et al. treated 24 patients with unresolving ARDS either with methylprednisolone or placebo. Steroids were begun if the Lung Injury Score (LIS) failed to improve by 1 point at day seven of respiratory failure. An initial intravenous loading dose of 2 mg/kg of methylprednisolone was given followed by a bolus of 0.5 mg/kg every 6 hours from day 1 to day 14. After day 14 methylprednisolone was tapered using a total dose of 1 mg/kg/d from day 15 to day 21, 0.5 mg/kg/d from day 22 to day 28, 0.25 mg/kg/d on days 29 and 30 and 0.125 mg/kg/d on days 31 and 32. On day 10 of treatment, the methylprednisolone group had an improved P_aO_2/F_iO_2 ratio (262 vs 148), a better Lung Injury Score (1.7 vs 3.0) as well as more successful extubations (7 vs 0). Mean duration of mechanical ventilation was 11.5 days in the treatment group vs 23 days in the placebo group. The outcome was improved with methylprednisolone. In the treatment group, 100% of patient survived the ICU admission and 87% of the hospital admission, vs 37% and 37%, respectively, of patients in the placebo group. A decrease in the plasma TNF- α , IL1- β , and IL-6 concentrations was observed in both groups, but the decrease was significantly higher and more sustained in the methylprednisolone group, hence providing supportive data for the presence of an endogenous glucocorticoid deficiency and a peripheral glucocorticoid resistance in unresolving ARDS [41]. Importantly, there was no significant difference in complications between the two groups [39].

Hydrocortisone in pneumonia

As in sepsis, the severity of community-acquired pneumonia is also related to the plasma inflammatory cytokine levels. Indeed, IL-1 β seems to be a marker of the severity of infection, IL-6 a marker of the severity of illness while TNF- α reflects the severity of pneumonia [42–44]. During severe community-acquired pneumonia, the leading cause of sepsis and septic shock, higher serum cytokine levels as well as a prolonged inflammatory response were correlated with a higher mortality [45, 46].

Confalonieri et al. hypothesized that low dose hydrocortisone administered in the early course of this disease may have the same positive effect on the outcome of severe community acquired pneumonia than during septic shock. In a multicenter, randomized, double-blind, placebo-controlled preliminary study,

46 patients admitted to the ICU because of severe community acquired pneumonia underwent corticosteroid replacement therapy [47]. Patients with clinical and radiographic evidence of pneumonia and either two minor or one major American Thoracic Society criterion for severe pneumonia were enrolled [48] (Table 3). Exclusion criteria were nosocomial pneumonia, acute burn injury, a preexisting medical condition with a life expectation of less than 3 months, as well as a condition requiring more than 0.5 mg/kg/d of prednisolone (acute asthma, chronic obstructive pulmonary disease). Hydrocortisone was administered as a 200 mg intravenous bolus followed by a continuous infusion of 10 mg/h during 7 days in parallel to the standard therapy. A diagnosis of adrenal insufficiency was not established. Primary endpoints were the improvement in P_aO_2/F_iO_2 , development of the multiple organ dysfunction syndrome (MODS) and delayed septic shock. Secondary endpoints were time duration of mechanical ventilation, length of ICU and hospital stay, as well as the hospital and 60 day survival. The trial was stopped after the inclusion of 46 patients because a significant improvement in P_aO_2/F_iO_2 and hospital mortality was achieved in the treatment group.

Indeed, at baseline, the mean P_aO_2/F_iO_2 was lower in the hydrocortisone group (141 in the hydrocortisone group vs 178 in the placebo group). At day 8, $P_aO_2/F_iO_2 > 300$ was obtained in 87% patients receiving hydrocortisone, while only 39% patients in the placebo group had a similar P_aO_2/F_iO_2 . The development of MODS was also prevented through the hydrocortisone treatment. Only 35% patients in the hydrocortisone group developed MODS vs 70% in the placebo group. Hydrocortisone also appeared to be protective against development of delayed septic shock as 9 (43%) patients in the placebo group needed vasopressors, while no such event was noted in the hydrocortisone group. The Duration of me-

Table 3 American Thoracic Society Criteria for severe pneumonia

Major Criteria	Minor criteria
1. Requirement of mechanical ventilation	1. Respiratory rate > 30 bpm
2. Increase in the size of opacities on chest radiograph of 50% or more in 48 h	2. $P_aO_2/F_iO_2 < 250$
3. Requirement of vasopressors > 4 hours	3. Bilateral or multilobar involvement on chest radiograph
4. Serum creatinine of 2 mg/dl or more	4. Systolic blood pressure ≤ 90 mmHg
	5. Diastolic blood pressure ≤ 60 mmHg
Severe pneumonia is defined clinical and radiographic evidence of pneumonia and 1 major criterion or 2 minor criteria	

chanical ventilation was reduced as the mean ventilation time was 10 days in the placebo group and 4 days in the treatment group. Furthermore, the ICU mortality (30% vs 0%) as well as the hospital (30% vs. 0%) and 60-day mortality (38% vs 0%) were significantly reduced in the hydrocortisone group. There was no difference in complications attributable to hydrocortisone in either group [47].

This study provides positive data about the use of low dose hydrocortisone in severe community-acquired pneumonia admitted to the ICU. However, these results should be considered carefully. Due to the small patient sample, the randomization failed to provide two homogeneous groups. Baseline P_aO_2/F_iO_2 was lower, mean CRP higher and the Chest Radiograph Score higher in the hydrocortisone group. Despite the current knowledge of the benefit of hydrocortisone in adrenal insufficiency, no screening for this condition was obtained. Hence there could be an imbalance in the two study groups with more adrenal insufficiency in the hydrocortisone treatment group which may explain their better results. Above all, the study was stopped early because of the perceived benefit. Considering the small sample group, the results have to be carefully evaluated. Although the mortality was significantly higher in the placebo group, very few incidents like one or two deaths in the treatment group, could have eliminated this difference. In conclusion, this preliminary study suggests a benefit of low dose hydrocortisone in severe community-acquired pneumonia but a larger trial with mortality as primary endpoint is necessary in order to confirm those results without major biases.

Glucocorticoid safety

Finally, it remains important to notice that low dose glucocorticoid treatment does not increase the risk of either gastroduodenal bleeding, superinfections or hyperglycemia as a large meta-analysis of 23 randomized and quasi-randomized trials proves [37].

Conclusion

Hydrocortisone should be used in sepsis and septic shock as several randomized, double-blind trials have shown a decrease of shock duration as well as an improved outcome. More recent trials have suggested a positive effect of this so-called replacement therapy in pneumonia and ARDS.

The mechanism for the hydrocortisone-induced benefit remains uncertain. In septic shock, it is assumed that an improved vasopressor responsiveness through the hydrocortisone treatment leads to a better outcome [49–51]. Recent data suggests that there is also a more proximal mechanism including the immune system. Multiple conditions such as severe pneumonia, sepsis or septic shock induce an exaggerated systemic inflammation with high IL-1, IL-6 and TNF- α levels. An impaired endogenous glucocorticoid production as found in adrenal insufficiency is unable to counterbalance the inflammatory response and may enhance severe tissue damage [33, 36, 52].

Hence adrenal insufficiency screening should be performed in every ICU patient with severe disease. More recent data show that adrenal insufficiency is not limited to pneumonia, ARDS, sepsis or septic shock. A high incidence of pituitary failure was also found in acute liver failure and post-liver transplantation [53]. Low dose hydrocortisone replacement may improve the outcome in those patients as well.

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