Review Articles

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Corticosteroids in sepsis and community-acquired pneumonia

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In this article

Abstract

Sepsis and septic shock, which are often caused by pneumonia, impact millions of people every year. Despite adequate antibiotic therapy, mortality remains high, up to 45% in septic shock, which is characterized by an inappropriate, excessive immune response of the host. Moreover, critical illness-related corticosteroid insufficiency often coexists. Against this background, several trials and meta-analyses evaluated corticosteroid therapy as adjuvant therapy with heterogeneous results. Indeed, before 2000, high-dosage, short courses of corticosteroid treatment resulted in no benefit on mortality and a higher rate of adverse events. After 2000, thanks to a deeper understanding of the pathophysiology, low-dosage with longer courses of treatment were tested. With this regimen, a faster decrease in inflammation and faster resolution of shock, with a low rate of mild adverse events, was demonstrated although no clear effect on mortality was shown. To date, guidelines on sepsis and septic shock and guidelines on severe community-acquired pneumonia suggest corticosteroid use in selected patients. Furthermore, by utilizing latent class analysis, phenotypes of sepsis patients who benefit the most from corticosteroid treatment were recently identified. Future research should be guided by a precision medicine approach to identify adequate dosage and duration of corticosteroid treatment for appropriate patients. This article is freely available.

Keywords
Antibacterial agents · Host immune response · Septic shock · Adjuvant drug therapy · Critical illness-related corticosteroid insufficiency

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Introduction

Every year sepsis impacts millions of people. Pneumonia is the most relevant cause of sepsis. Rapid, appropriate antibiotic treatment is a cornerstone in the management of these diseases. Unfortunately, despite adequate therapy, mortality often remains high, up to 45% in septic shock. This is also probably due to an excessive, uncontrolled immune response of the infected host. Corticosteroids are a class of drugs with immunoregulatory and mineralocorticoid properties, which, therefore, have been hypothesized to be helpful as adjuvant therapy in sepsis and community-acquired pneumonia.

Definitions and epidemiology

Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, is characterized by an increase in Sequential Organ Failure Assessment (SOFA) score of 2 points. Septic shock is a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities. Vasopressors to maintain a mean arterial pressure $\geq 65\,mm\,Hg$ and a serum lactate level $> 2\,mmol/L$ despite volume

resuscitation are required to define septic shock [26]. Each year, sepsis and septic shock impact millions of people and result in a mortality rate of between 16 and 33% among those affected [9]. The most common cause of sepsis and septic shock is pneumonia, accounting for up to 50% of cases.

Community-acquired pneumonia (CAP) is a common respiratory infectious disease that leads to hospitalization in up to 40% of patients. Five percent of hospitalized CAP patients suffer severe CAP and require care in an intensive care unit (ICU) [18].

Extremely poor outcomes in about half of the sepsis and severe pneumonia cases warrant the need for improving therapies.

Corticosteroid rationale

Cortisol, the most important physiologically synthesized glucocorticoid in the adrenal glands, is produced upon stimulation by adrenocorticotropic hormone. It circulates in the plasma, with 80–90% bound to corticosteroid-binding globulin (CBG) and the rest either unbound or bound to albumin. These lipophilic hormones diffuse across cell membranes and bind to glucocorticoid receptors (GRs). The GRs are typically found in the cytoplasm. Among the GRs, GR-α plays a major role in mediating stress and inflammation responses. Once bound with cortisol, GR-α undergoes a structural change that allows it to enter the cellular nucleus. There, it can bind to glucocorticoid-response elements and activate or repress the expression of pro-inflammatory genes, including various transcription factors such as nuclear factor-kappa B (NF-κB), which plays a crucial and generalized role in inducing cytokine gene transcription. Indeed, the glucocorticoid–GRα complex plays an important role in maintaining homeostasis and adapting to stressors by affecting the activity of thousands of genes involved in stress and nonstress responses [5]. Glucocorticoids can exhibit some faster anti-inflammatory effects through non-genomic pathway by activating kinase pathways. Endothelial GR acts as a critical negative regulator of nitric oxide (NO) and NF-κB release [12].

Systemic inflammation is a complex response of the innate immune system to infectious and noninfectious threats. While controlled inflammation is beneficial, excessive or prolonged inflammation can lead to tissue damage and disease. Critical illness-related corticosteroid insufficiency (CIRCI), defined in 2008 by a Task Force of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, is a condition characterized by dysregulation of the hypothalamic–pituitary–adrenal axis, altered cortisol metabolism, and tissue resistance to glucocorticoids. CIRCI is present in conditions such as sepsis and pneumonia [17].

Corticosteroid (CS) therapy in patients with CIRCI is hypothesized to have potential benefits. It may reduce circulating proinflammatory cytokines levels, turning off excessive inflammation. In addition, CSs can enhance cardiovascular function by boosting mineralocorticoid activity to increase effective blood volume and systemic vascular resistance, with a portion of this effect being linked to endothelial GR and NO regulation.

Evidence in literature

Since 1950, several randomized controlled trials (RCTs) on the efficacy and the safety of CS treatment in sepsis and pneumonia have been published. Trials conducted before 1998 using a "short-course high-dosage" regimen (i.e., 2 g equivalent of hydrocortisone given over 24 h) showed detrimental effects on mortality and other outcomes [16]. However, newer trials designed after the 1990s adopted a "long-course low-dosage" approach, thanks to a deeper comprehension of pathophysiology.

◘ Table 1 summarizes the characteristics of the most relevant RCTs conducted after this change in drug regimen. Only placebo-controlled RCTs that enrolled more than 100 patients have been included. These trials were mostly multicentric but displayed significant heterogeneity due to evolving definitions of syndromes, varying inclusion criteria, different types of CSs and their combinations, diverse treatment regimens and durations, and different reported outcomes. Indeed, six RCTs included patients with septic shock [3, 4, 13, 28, 29, 31]: one included patients with severe sepsis

and excluded shocked patients [15], and seven focused on CAP [6, 8, 19, 20, 27, 30, 32]. All RCTs that included patients suffering sepsis or septic shock evaluated hydrocortisone as the CS of choice. In two studies [3, 4], oral fludrocortisone was added to hydrocortisone treatment to increase mineralocorticoid activity. In one RCT [31] was deliberately chosen not to use fludrocortisone after that a study by Annane et al. [7] failed to demonstrate superiority of the combination of those two CSs rather than hydrocortisone alone. In other RCTs enrolling CAP patients, only one tested hydrocortisone [8], while methylprednisolone [19, 30] and dexamethasone [20, 32] were the treatment drug in two studies, and prednisolone [27] and prednisone [6] was used once. The latter CSs are characterized by longer half-life, higher glucocorticoid, and lower mineralocorticoid activity. Furthermore, methylprednisolone reaches higher concentrations in the lungs [14]. In ◘ Table 1, we have reported glucocorticoid equivalent dosages administered. Treatment lasted for 5 or 7 days in most of the RCTs. When CSs were administered for more than 1 week, the study design included a scheme to de-escalate treatment. Two RCTs [4, 28] contemplated performing a high-dosage 250 μg corticotropin test to identify patients who should have better responded to CS treatment and, thus, to define responder (R) and nonresponder (NR) cohorts in order to evaluate the primary outcome. This procedure, although suggested in the first version of CIRCI guidelines [17], never entered clinical practice. Currently, the newest version of Surviving Sepsis Campaign (SSC) guidelines [9] does not comment on this.

The outcomes explored were also very heterogeneous. ◘ Figure 1 shows the odds ratios of 28-day mortality and ICU and hospital length of stays in the two cohorts of patients. Half of the RCTs showed differences in primary outcomes. In sepsis and septic shock trials, Annane et al. initially found a reduction in 28-day mortality for nonresponders but not responders, indicating a lower risk of death in the CS-treated patients during the first 28 days. In a subsequent study, enrolling more than 1200 patients, Annane et al. demonstrated

Table 1 Randomized controlled trials (RCTs) evaluating corticosteroid treatment in sepsis and CAP patients

First author, year	Population	Sites	Patients	Steroid	Dosage	Equivalent dosage[a]	Duration (days)	Primary outcome	Primary outcome result
Annane, 2002 [4]	Septic shock	19	300	HC FC	HC 50 mg iv q6h, FC 50 µg po q6h	200	7	28-day mortality in NR patients	63% death in placebo vs 53% in treatment group. HR 0.67 (0.47–0.95), $p = 0.02$
Sprung, 2008 [28]	Septic shock	52	499	HC	50 mg iv q6h for 5 days, 50 mg iv q12h for 3 days, 50 mg iv q24h for 3 days	200, then 100, then 50	11	28-day mortality in NR patients	ND
Snijders, 2010 [27]	CAP	1	213	PDNL	20 mg po/iv q24h	80	7	Clinical cure[b] at day 7	ND
Meijvis, 2011 [20]	CAP	2	304	DM	5 mg iv q24h	125	5	Hospital LOS	Shorter hospital LOS in treated: 6.5 vs 7.5 days, $p = 0.048$
Torres, 2015 [30]	Severe CAP + CRP > 150 mg/L	3	120	MP	0.5 mg/kg iv q12h	200[c]	5	Treatment failure rate[d]	Less failure in treated: 13% vs 31%, $p = 0.02$. Fewer cases of late treatment failure
Blum, 2015 [6]	CAP	7	785	PDN	50 mg iv q24h	200	7	Time to clinical stability[e]	Shorter time to clinical stability in treated: 3.0 vs 4.4 days, HR 1.33 (1.15–1.50), $p < 0.001$
Tongyoo, 2016 [29]	Sepsis or septic shock + ARDS	1	197	HC	50 mg iv q6h	200	7	28-day mortality	ND
Gordon, 2016 [13]	Septic shock	18	409	HC	50 mg iv q6h for 5 days, 50 mg iv q12h for 3 days	200, then 100, then 50	11	28-day kidney failure-free days[f]	ND
Keh, 2016 [15]	Severe sepsis	34	353	HC	EI: 200 mg for 5 days, 100 mg for 2 days, 50 mg for 2 days, 25 mg for 2 days	200, then 100, then 50, then 25	11	Development of septic shock	ND
Annane, 2018 [1]	Septic shock	34	1241	HC FC	HC 50 mg iv q6h, FC 50 µg po q6h	200	7	90-day mortality	Lower 90-day mortality in treated: 43.0 vs 49.1%, $p = 0.03$, RR 0.88 (0.78–0.99)
Venkatesh, 2018 [31]	Septic shock + MV	69	3800	HC	200 mg iv EI	200	7	90-day mortality	ND
Wittermans, 2021 [32]	CAP	4	412	DM	6 mg po q24h	150	4	General Ward LOS	Shorter LOS in treated: 4.5 vs 5 days, $p = 0.033$

Table 1 (Continued)

First author, year	Population	Sites	Patients	Steroid	Dosage	Equivalent dosage[a]	Duration (days)	Primary outcome	Primary outcome result
Meduri, 2022 [19]	Severe CAP	42	586	MP	40 mg iv, then EI: 40 mg for 7 days, 20 mg for 7 days, 12 mg for 3 days, 4 mg for 2 days	200, then 100, then 60, then 20	20	60-day mortality	ND
Dequin, 2023 [8]	Severe CAP	31	795	HC	200 mg iv for 4 days, then tapered in 4 or 10 days according to prespecified plan based on patient's improvement	200	200	28-day mortality	Lower 28-day mortality in treated: 6.2 vs 11.9%, absolute reduction −5.6%, $p = 0.006$

HC Hydrocortisone, *FC* Fludrocortisone, *PDNL* Prednisolone, *PDN* Prednisone, *DM* Dexamethasone, *MP* Methylprednisolone, *ND* No difference, *q(x)h* every (x) hours, *iv* intravenous, *po* orally, *EI* 24 h extended infusion, *NR* Nonresponder (< 9 μg/dL) to a high-dosage corticotropin test (250 μg iv bolus), *LOS* Length of stay, *CAP* Community-acquired pneumonia, *ARDS* Acute respiratory distress syndrome, *HR* hazard ratio, *RR* risk ratio

a Calculated as mg of glucocorticoid equivalent

b Cure defined by: resolution or improvement of symptoms and clinical signs related to pneumonia without the need for additional or alternative therapy

c Calculated for an 80 kg adult

d Composite outcome of early and treatment failure, or both. Early failure defined as 1) development of shock, 2) need for invasive mechanical ventilation not present at baseline 3) death within 72 h of treatment. Late failure defined as 1) radiographic progression, 2) persistence of severe respiratory failure, 3) development of shock, 4) new need for invasive mechanical ventilation, 5) death between 72 and 120 h after treatment initiation

e Defined as temperature < 37.8 °C, heart rate < 100 bpm, respiration rate < 24 bpm, systolic blood pressure (SBP) < 90 mm Hg without vasopressor support, normal mental status, ability for oral intake, and oxygen partial pressure (PaO_2) ≥ 60 mm Hg or oxygen saturation (SpO_2) ≥ 90%

f Defined as Acute Kidney Injury Classification (AKIN) stage 3

higher 90-day survival in the CS-treated cohort [3]. On the other hand, the three RCTs by Sprung [28], Tongyoo [29] and Ventakesh [31] failed to assess the impact of treatment on 28-day or 90-day mortality. Disease severity may have contributed to these different results, i.e., trials by Annane et al. included more severely ill patients, as demonstrated by higher SOFA score (i.e., 12 ± 3 vs 10 ± 2) and higher overall mortality (i.e., up to 50% vs less than 35%).

Most of the studies conducted on CAP patients have clinical cure or treatment failure as the primary outcome. Torres et al. [30] performed a RCT with a severe CAP population characterized by high inflammation (C-reactive protein < 150 mg/L) and, they demonstrated a reduction of treatment failure from 31% to 13% in patients treated with methylprednisolone, mainly due to a lower rate of late treatment failure. Similarly, but including not only severe patients, Blum et al. [6] described faster time to clinical cure in CS-treated patients. However, in the RCT conducted by Snijders et al. [27], no effect of CSs on the rate of patients clinically cured after 7 days of treatment was detected. Less severity of CAP of the population enrolled and the lower equivalent dosage of CS could explain differences in results. In addition, Wittermans et al. [32] and Meijvis et al. [20] showed that a short course of orally or intravenously administered dexamethasone slightly, but statistically, reduced general ward and in-hospital length of stay in CAP patients. Interestingly, the only RCT on CAP patients which demonstrated a mortality (28-day) reduction is the recent study by Dequin et al. [8], where patients received either hydrocortisone as the CS of choice or placebo. Notably, all positive results regarding CS adjunctive therapy in CAP are on short-term outcomes. Indeed, the largest RCT conducted in CAP patients did not find an effect on 60-day mortality [19].

Interestingly, CS treatment was associated with various secondary outcomes, including improvement in gas exchange in mechanically ventilated patients [3, 29] and faster vasopressor withdrawal [3, 4, 31], inflammatory cytokines reduction, and resolution of fever [20, 27]. A subanalysis in non-severe CAP patients indicated
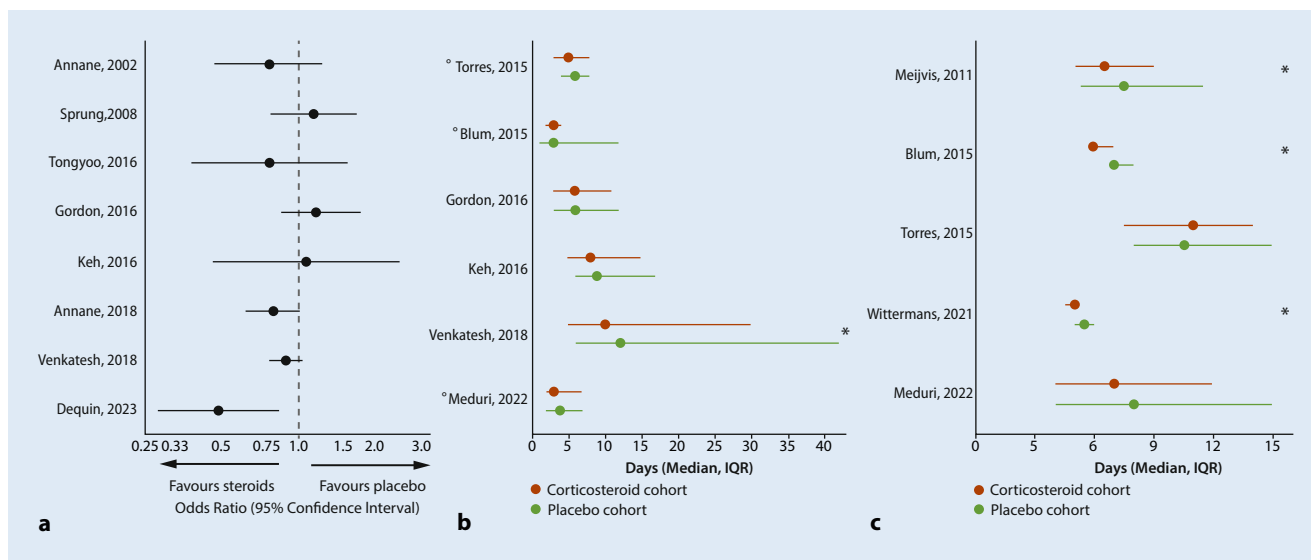
Fig. 1 ▲ Major outcomes in randomized controlled trials evaluating corticosteroid treatment in sepsis and community-acquired pneumonia patients. **a** Odds ratios (95% confidence interval) of 28-day mortality in corticosteroid-treated patients. Median (interquartile range [IQR]) intensive care unit (**b**) and hospital (**c**) length of stay in both cohorts. * statistically significant difference reported in the original trial. ° considering only CAP patients who required ICU admission

a higher occurrence of late treatment failure with CS treatment [27]. In addition, Keh et al. [15] failed to demonstrate lower progression from sepsis to septic shock in patients treated early with CS.

Several metanalyses were performed to assess CS treatment effects in sepsis and septic shock, yielding heterogenous results. In their meta-analyses, Annane et al. [1] and Fang et al. [10] concluded that CS had beneficial effects on the resolution of shock, 28-day mortality, as well as ICU and hospital length of stay. Moreover, Annane et al. [1] noticed that survival benefits were dependent on the dose of corticosteroids (the lower the dose for a longer duration of treatment, the better) and on the severity of illness (the more severely ill the patients were, the greater the benefit from treatment). However, although Rygard et al. [24] and Gibbison et al. [11] failed to find a survival benefit on 90- and 28-days mortality or an effect on length of stay attributable to CS treatment, both agreed in concluding that CSs favor shock resolution.

Viral CAP deserves a different discussion. Indeed, for coronavirus disease 2019 (COVID-19) oxygen-requiring pneumonia and acute respiratory distress syndrome (ARDS) patients, low-dose dexamethasone for 10 days became standard treatment [23]. Whereas, a propensity-matched retrospective study [22] showed higher mortality in severe influenza CAP patients treated with CSs.

Adverse events

Long-term steroid therapy in patients with autoimmune or lung diseases is known to be associated with certain toxicities. Although CSs use in sepsis and CAP is typically shorter, potential adverse events (AEs) have been evaluated in trials and meta-analyses.

The most common AE reported in the CS treatment group was hyperglycemia [3, 6, 8, 15, 20, 28, 29, 32], but it did not have an impact on outcomes in the various trials. The study by Venkatesh et al. [31] reported a higher percentage of AE in the CS group than in the placebo group (1.1% vs. 0.3% of included patients, $p = 0.009$). Another trial [28] showed higher hypernatremia and superinfection rates in CS-treated patients. These results are partially confirmed by meta-analyses. Indeed, three studies [1, 10, 24] reported a higher incidence of hyperglycemia and hypernatremia in the CS treatment group. These studies and that of Gibbison et al. [11] did not report a higher risk of superinfection. Nevertheless, as highlighted by CIRCI guidelines [2], glucocorticoid treatment blunts febrile response to superinfec-

tion; therefore, strict surveillance is highly recommended.

Finally, no differences in rates of gastrointestinal bleeding and neuromuscular weakness were detected in these studies.

Conclusions and future perspectives

Despite the demonstrated safety of corticosteroid (CS) therapy, different results persist in effects on outcomes in sepsis and pneumonia. Accordingly, the Surviving Sepsis Campaign (SSC) guidelines [9] suggest using CS (hydrocortisone, 50 mg intravenously, every 6 h) only in adult patients with septic shock and an ongoing requirement for vasopressors (at least 4 h after initiation of norepinephrine or epinephrine ≥ 0.25 µg/kg/min). In addition, guidelines for severe community-acquired pneumonia [18], accordingly to SSC guidelines, suggest CS treatment (methylprednisolone, 0.5 mg/kg intravenously, every 12 h, for 5 days) in CAP patients suffering from shock, except for those with a confirmed viral origin (e.g., influenza, severe acute respiratory syndrome [SARS], Middle east respiratory syndrome [MERS]). The different results observed in randomized controlled trials (RCTs) may be attributed to the intrinsic heterogeneity of the diseases, including different pathogens, host

immune responses, and severity levels. In the future, it is imperative to enhance the effectiveness of interventions by carefully identifying eligible patients through a precision medicine approach. More recently, utilizing latent class analysis, specific phenotypes of sepsis can be identified [25]. In addition, advancements in drug delivery, i.e., to precisely deliver steroids to target tissues, hold promise in this field of research [21]. Precision medicine is not limited to identifying phenotypes but will also involve customizing the dosage and duration of CS treatment and also its precise delivery to specific cells or tissues.

Practical conclusion

- Trials evaluating corticosteroid use in sepsis and community-acquired pneumonia have had heterogeneous results. Discrepancies between studies may be explained by multiple factors such as differences in causes of sepsis, dose, timing of initiation, duration, modalities of treatment cessation, and corticosteroid type.
- Patients suffering from septic shock unresponsive to fluid resuscitation and necessitating high amine dosage are suggested to be treated with hydrocortisone 50 mg intravenous every 6 h rather than methylprednisolone.
- Long-course low-dosage corticosteroid administration was effective in faster resolution of inflammation and shock, rather than short-course high-dosage. Effects on mortality have not been demonstrated.
- It has been reported that start of hydrocortisone during the first 24 h of shock was associated with lower in-hospital, more vasopressor-free days and shorter intensive care unit length of stay compared to later start.
- In this setting, corticosteroid therapy is safe, and a low rate of mild adverse event has been reported.
- Future research should follow a precision medicine approach and focus on identifying the characteristics of patients who will benefit most from corticosteroid therapy.

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Zusammenfassung

Kortikosteroide bei Sepsis und ambulant erworbener Pneumonie

Sepsis und septischer Schock, die oft durch eine Pneumonie verursacht werden, betreffen jedes Jahr Millionen Menschen. Trotz adäquater antibiotischer Therapie bleibt die Mortalität hoch, bis zu 45 % beim septischen Schock, der durch eine unangemessene, exzessive Immunantwort des Wirts charakterisiert ist. Außerdem besteht häufig gleichzeitig eine mit einer kritischen Erkrankung einhergehende Kortikosteroidinsuffizienz. Vor diesem Hintergrund wurde die Kortikosteroidbehandlung in verschiedenen Studien und Metaanalysen als adjuvante Therapie untersucht – mit heterogenen Ergebnissen. So ergab, vor dem Jahr 2000, die hoch dosierte, kurzzeitige Kortikosteroidbehandlung keinen Nutzen in Bezug auf die Mortalität und eine höhere Rate an Nebenwirkungen. Nach 2000 wurde, dank einem tiefer gehenden Verständnis der Pathophysiologie, die niedrig dosierte längere Kortikosteroidbehandlung untersucht. Mit diesem Schema wurde ein schnellerer Rückgang der Entzündungsprozesse und eine schnellere Behebung des Schocks bei einer geringen Rate leichtgradiger Nebenwirkungen nachgewiesen, auch wenn es keine eindeutigen Auswirkungen auf die Mortalität gab. Bisher wird in Leitlinien zu Sepsis und septischem Schock sowie in Leitlinien zu schwerer ambulant erworbener Pneumonie der Einsatz von Kortikosteroiden bei ausgewählten Patienten empfohlen. Vor Kurzem wurden mittels der latenten Klassenanalyse Phänotypen von Sepsispatienten identifiziert, die am meisten Nutzen aus der Kortikosteroidtherapie ziehen können. Zukünftige Studien sollten sich an einem präzisionsmedizinischen Ansatz orientieren, um die adäquate Dosierung und Dauer der Kortikosteroidtherapie für die entsprechenden Patienten zu ermitteln.

Schlüsselwörter
Antibakterielle Wirkstoffe · Wirtsimmunantwort · Septischer Schock · Adjuvante medikamentöse Therapie · Kortikosteroidinsuffizienz bei kritisch Kranken