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Review

Corticosteroids in sepsis

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ABSTRACT

Sepsis is a major health and socioeconomic burden worldwide. Although international guidelines have helped reduce crude mortality rates from sepsis by optimizing infection control and support of vital organ function, there are still no specific therapies for sepsis, other than corticosteroids. The aims of this narrative review were to provide readers with the most recent data on corticosteroids, as well as up-to-date evidence regarding their effects in patients with sepsis. Corticosteroids regulate the function of most cell types involved in host response to infections, through both genomic and non-genomic effects, reprogramming immune cells (via regulation of mitochondrial metabolism) toward anti-inflammatory types, restoring endothelial cell function and endothelium integrity, facilitating epithelium repair, and restoring vascular smooth muscle function, as well as organ perfusion. In patients with sepsis, these effects are achieved using supraphysiological doses of corticosteroids, equating to approximately 200 mg/day of hydrocortisone equivalent for 5–15 days, depending on the clinical context. The molecular and cellular effects of corticosteroids translate into prevention and reversal of the need for vasopressor, respiratory, and renal supportive therapies, as well as acceleration of organ function resolution, shorter intensive care unit (ICU) and hospital stays, and improved short- and mid-term survival. Remaining gaps in knowledge and evidence to inform practice include insufficient data about the effects of corticosteroids in children, a lack of reliable biomarkers to distinguish those patients who can benefit from treatment, and inadequate information about the effects of corticosteroids on the long-term sequelae of sepsis.

The Burden of Sepsis

The social, economic, and health burdens of sepsis, which is defined as life-threatening organ dysfunction triggered by an abnormal host response to invading microorganisms,[1] are heavy worldwide. Among organisms that cause sepsis, *Streptococcus pneumoniae, Streptococcus aureus, Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* account for more than two-thirds of cases, and there is a high prevalence of multidrug resistance.[2,3] Although sepsis is a major threat to EU and US populations, it disproportionally affects the most vulnerable and low- and middle-income populations, with approximately 50 (3.4 in EU) million cases and 11 (0.68 in EU) million deaths annually.[4] Given population growth and aging, cases of sepsis are predicted to double by 2050.[2] Furthermore, around three-quarters of patients who survive for 3 years after sepsis develop new health problems, with annual costs of €6.8 billion.[5] In 2017, almost half of all sepsis cases globally occurred in children, with approximately 20 million cases and 2.9 million deaths in children aged <5 years. Analysis of the 2016 Kids' Inpatient Database (KID) dataset in the US identified 12,297 patients of 0–21 years old with sepsis admitted to 1253 hospitals, and determined a crude mortality rate of 14.6 %.[6] Risk of death differed according to patient ethnicity, geographic region, and insurance status.[7] At 12 months following pediatric intensive care unit (ICU) admission for septic shock, 13 % of patients had died, and 35 % of surviving patients had not regained their previous quality of life.[8] In the European Union Childhood Life-threatening Infectious Disease Study (EUCLIDS) study of 2844 patients aged 1 month to 18 years, the main sources of sepsis were pneumonia (18 %), central nervous system (17 %), and soft tissue infection (9 %), and

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causal microorganisms included *Neisseria meningitidis* (9%), *S. aureus* (8%), *S. pneumoniae* (8%), and group A streptococcus (6%).[9] In 2017, the World Health Organization urged state members to act. Evidence-based guidelines,[10] including early source control, antimicrobials, and vital organ function support, have contributed to a reduction in sepsis mortality.[11] With the exception of corticotherapy in patients with septic shock,[12,13] no specific interventions are available for sepsis.[10,14] Hyper- and hypo-inflammation are concurrent, sustained, and vary according to pathogen and host characteristics.[15,16] Key challenges include the provision of dynamic characterization (prediction) of individual risks and response to treatments (treatable traits).[17,18]

The Pharmacological Basis of Corticotherapy for Sepsis

A recent review has summarized 75 years of discoveries about the molecular mechanisms of action of corticosteroids.[19] Corticosteroids act via their receptors: glucocorticoid receptor (GR), encoded by the *NR3C1* gene, and mineralocorticoid receptor (MR), encoded by *NR3C2*. While GR is present in almost all cells, MR only binds glucocorticoids in kidney and brain.[19] Inactive GR resides in the cytoplasm, stabilized by chaperone proteins, while the glucocorticoid–GR complex traps nuclear factor-kappaB (NF-κB) in the cytoplasm, preventing its nuclear translocation. The main active GR isoform, GR alpha, comprises 777 amino acids with the following domains: an N-terminal transactivation domain, activation domain 1, a DNA-binding domain, and a ligand-binding domain, and activation domain 2. After translocation to the nucleus, activated GR proceeds through a stepwise process, starting from binding to DNA at GR binding sites, followed by recruitment of coregulators (including nuclear receptor coactivators 1–3 and nuclear receptor corepressors 1–2). Next, GR monomers inhibit the proinflammatory transcription factors, NF-κB and AP1, thereby repressing expression of their downstream genes (transrepression), while GR dimers binds to glucocorticoid responsive elements (GRE) to induce (transactivate) or negative GRE to inhibit gene expression. There are also other GR monomer binding sites, and tetrameric GR complexes can also bring two glucocorticoid binding sites together.[20,21] Beyond the transrepression through GR monomers and transactivation by GR dimers, activated GR also upregulates the Dusp1,[22] Anxa1,[23] Gilz,[24] and A20[25] anti-inflammatory genes.

Glucocorticoids also have rapid non-genomic effects, resulting from their interactions with membrane sites, the chaperone proteins that are released when glucocorticoids bind to GR, or from phosphoinositide 3-kinase competition.[26]

The main effects of corticosteroids relevant to their application in patients with sepsis are summarized in Table 1. The molecular effects of corticosteroids are cell-type specific.[27] At the level of adaptive immunity, glucocorticoids inhibit polarization toward T helper (TH) 1 and TH17 cells and corresponding proinflammatory cytokines, while increasing polarization toward TH2 cells.[28] Furthermore, they increase apoptosis and decrease signaling by TH cells, cytotoxic T cells, and B cells, while upregulating B cell production of B lymphocyte-induced maturation protein 1 and interleukin (IL)-10. Glucocorticoid effects on innate immunity include: (1) decreasing Toll-like receptor signaling in mast cells, macrophages, basophils, and eosinophils; (2) increasing histamine release from mast cells; (3) polarization of macrophages toward type 2, with decreased proinflammatory cytokine production, increased release of anti-inflammatory molecules, and elevated phagocytosis activity; (4) increasing neutrophil production; and (5) increasing apoptosis of basophils and eosinophils. Glucocorticoids also increase natural killer cell activation and dendritic cell apoptosis, while inhibiting their maturation and capacity to produce proinflammatory cytokines and present antigen.

The role of glucocorticoids in immune cell metabolism has recently been unraveled.[29,30] Glucocorticoids reprogram inflammatory macrophages into anti-inflammatory cells by modulating mitochondrial function, inhibiting glycolysis and hypoxia-induced factor 1 alpha, and stimulating itaconate, which counteracts succinate accumulation resulting from stalling of the tricarboxylic acid cycle. The effects of glucocorticoids in restoring the mitochondrial network are GR-dependent and mainly non-genomic via GR interaction with pyruvate dehydrogenase.[31]

Preclinical Evidence for Corticosteroid Use in Sepsis

In various animal models (rabbits and dogs), structural smooth muscle alterations that cause decreased vasomotor tone are fully reversed by dexamethasone, with subsequent restoration of norepinephrine contractility.[32] These beneficial effects of dexamethasone vary according to its pharmacological formulation, with disodium phosphate ester having substantial effects, while sodium sulfate ester was ineffective.[33] Methylprednisolone is also reported to have cardiovascular protective effects in primates challenged with intravenous endotoxin.[34] Furthermore, the protective cardiovascular effects of corticosteroids have been demonstrated at the regional circulation level in the liver,[35,36] gut,[37] brain,[38] lung,[39] and kidney.[40] The mechanisms underlying the cardiovascular protection exerted by corticosteroids include: (1) facilitation of neuronal excitability, with enhancement of central sympathetic outflow;[41] (2) decreased in sepsis-induced vascular permeability[42,43] (3) inhibition of nitric oxide synthase,[44] group II secretory phospholipase A2,[45] cyclooxygenase metabolites,[46] endothelin-1,[47] ATP-sensitive potassium channels,[48] and NF-κB;[49] and (4) upregulation of adrenomedullin,[50] the RhoA/ RhoA kinase (ROCK), extracellular signal-regulated kinase (ERK), and p38 signaling pathways,[51] and norepinephrine-induced shrinkage and actin cytoskeleton rearrangement.[52]

Preclinical evidence for attenuation of inflammation in sepsis by corticosteroids is also abundant.[53–56] Methylprednisolone can restore phagocytic and opsonin activities in the reticuloendothelial system.[53] Furthermore, glucocorticoids preserve neutrophil function in dogs with *E. coli* sepsis,[54] inhibit the release and lethality of tumor necrosis factor and IL-1 in mice,[55] reduce Kupffer cells (a major source of cytokines in sepsis),[56] lower plasma hydrogen sulfide concentration,[57] prevent and reverse NF-κB expression,[58] reduce mitochondrial injury, but preserved cytochrome c oxidase, and suppress proapoptotic proteins,[59] reverse lipopolysaccharide (LPS)-induced Toll-like receptor 4 and myeloid differentiation factor 2 expression,[60] and suppress dendritic cell release of IL-12.[61] Together, the effects of corticosteroids on the cardiovascular system and in-

Table 1
Summary of corticosteroid effects.

Systems/functions		Molecular/cellular	Preclinical	Clinical
Immunity	Adaptive	Inhibit polarization toward TH1 and TH17 Increase polarization toward TH2 Increase apoptosis and decrease signaling of cytotoxic T and B cells Upregulate B cell formation Upregulate IL-10 Decrease TLR signaling Increase histamine release Polarization toward type 2 macrophages Decrease proinflammatory cytokines Increase anti-inflammatory cytokines and phagocytic activities increase neutrophil production and NK cell activation Increase apoptosis of dendritic cells and decrease their function	Restore the reticuloendothelial system, phagocytic, and opsonin activities Preserve neutrophil function Decrease Kupfer cells Reverse LPS induced TLR4 and MD2 expression levels Prevent and reverse NF-κB expression Inhibit TNF and IL-1 Suppress dendritic cell release of IL-12 Protect the mitochondria by preserving cytochrome c and suppressing proapoptotic proteins	Increase in plasma levels of CXCL9 and CXCL10, and of granzymes A and B Modulate release of soluble adhesion molecules Decrease neutrophil activation Decrease plasma levels of IL-6, IL-1, and IL-8 Decrease plasma levels of soluble TNF receptors 1 and 2, and of IL-10
	Metabolism	Modulation of mitochondrial function Inhibit glycolysis and hypoxia-induced factor 1 alpha Stimulate itaconate Inhibit succinate accumulation Stalling of the tricarboxylic acid cycle		
Cardiovascular function		Facilitate neuronal excitability Increase central sympathetic outflow Upregulate adrenomedullin, RhoA/ROCK, ERK, and p38 signaling, norepinephrine shrinkage of nucleus, and rearrangement of the cytoskeleton Decrease vascular permeability Inhibit inducible NO synthase, cyclooxygenase 2, phospholipase, and ATP-sensitive K^+ channels	Increase vasomotor tone Increase sensitivity to norepinephrine	Restore vascular responsiveness to norepinephrine, vasopressin, and angiotensin 2 Accelerate weaning from vasopressors Prevent the need for vasopressor initiation in CAP
			Reverse LPS/sepsis-induced alterations in kidney, liver, lung, gut, and brain regional circulation, and decrease immune cell infiltration and inflammation Reduce mortality	Accelerate weaning from respiratory support Prevent the need for respiratory support in CAP Reduce the need for renal replacement therapy Accelerate resolution of organ function, as assessed by SOFA scores Reduce length of hospital stay Reduce mortality

CAP: Community-acquired pneumonia; ERK: Extracellular signal-regulated kinase; IL: Interleukin; LPS: Lipopolysaccharide; NK: Natural killer; NO: Nitric oxide; SOFA: Sequential organ failure assessment; TH1: T helper 1; TLR: Toll-like receptor; TNF: Tumor necrosis factor.

flammation translate into prevention or restoration of organ damage and function,[59,62,63] as well as survival in various animal models.[35,64,65] In experimental sepsis, the favorable effects of corticosteroids are modulated by numerous factors, among which is macrophage migration inhibitory factor[66] and triggering receptor expressed on myeloid cells-2[67] have negative regulatory effects, while IL-10[68] and Gilz[69] exhibit positive regulatory activity. Preclinical studies also suggest a critical role for endothelial expression of GR[70] and MR.[71]

Clinical Evidence for Corticosteroid Use in Sepsis

Corticosteroids reverse cardiovascular failure

In healthy volunteers, endotoxin-induced hyporesponsiveness to incremental doses of norepinephrine, and this was prevented by intravenous administration of hydrocortisone.[72] Endotoxin-induced endothelial dysfunction is, at least partly, related to the effects of proinflammatory mediators (e.g., tumor necrosis factor [TNF], IL-1, IL-6, and cyclooxygenase), and inhibition of these mediators by corticosteroids may explain the restoration of norepinephrine responsiveness.[73] Hydrocortisone can also restore blood pressure response to alpha1 agonists in patients with septic shock,[74,75] and enhances pressure sensitivity to catecholamines, which translates into accelerated vasopressor withdrawal in this context.[12,76–79] Analysis of pooled data from 18 trials (n=6938 participants) revealed a risk ratio (RR) for shock reversal at day 7 of 1.22 (95 % confidence interval [CI]: 1.13 to 1.33, P <0.00001) and of 1.05 (95% CI: 1.03 to 1.07, P <0.00001) at day 28 in favor of corticosteroids relative to placebo or usual care.[80] Furthermore, hydrocortisone prevented the need for vasopressor therapy in patients with community-acquired pneumonia-related sepsis,[81] but not in those with unselected sepsis.[82]

Corticosteroids attenuate inflammation

In healthy volunteers challenged with LPS, prednisolone acts in a dose-dependent manner to prevent increases in plasma concentrations of the chemokines, CXCL9 and CXCL10, and of

granzyme A and B levels,[83] as well as influencing the release of soluble endothelial adhesion molecules.[84] In patients with septic shock, corticosteroids hasten the decrease in circulating IL-6,[85–87] IL-1,[86] and IL-8.[87,88] Furthermore, hydrocortisone reduced endothelial cell (soluble E-selectin) and neutrophil (expression of CD11b, CD64) activation, and reduced the anti-inflammatory response (i.e., soluble tumor necrosis factor receptors I and II and IL-10).[87] In peripheral blood monocytes, human leukocyte antigen-DR expression was only slightly depressed in response to hydrocortisone, whereas *in vitro* phagocytosis and levels of the monocyte-activating cytokine, IL-12, increased.[87] Furthermore, premature withdrawal of hydrocortisone resulted in a rebound in inflammation and vasopressor dependency.[87]

Corticosteroids reverse organ failure

In patients with septic shock, corticosteroids improve the partial pressure of oxygen /fraction of inspired oxygen (PaO_2/FiO_2) ratio[85] and accelerate ventilator weaning.[12,77–79] Similarly, corticosteroids prevent ventilator dependency in patients with community-acquired pneumonia-related sepsis.[85] In a secondary analysis of the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial, the odds ratio for the need for renal replacement therapy was 0.84 (95 % CI: 0.70 to 0.99; *P*=0.04), in favor of hydrocortisone therapy as compared to placebo.[89] Analysis of pooled data from 17 trials (*n*=3220 participants) detected *a* −1.27 (95 % CI: −1.63 to −0.92, *P* <0.00001) mean difference in Sequential Organ Failure Assessment **(**SOFA) score at day 7 in favor of corticosteroids compared to placebo or usual care.[80]

Corticosteroids reduce length of hospital stay and mortality

Individual trials have reported variable effects of corticosteroids on short-term (up to 90 days) mortality in adults with septic shock.[12,77–79] Two trials of hydrocortisone plus fludrocortisone reported significant reductions in mortality,[12,77] while another two trials found no evidence that hydrocortisone reduced mortality.[78,79] Analysis of the best evidence from pooled data from the literature for mortality at 28 days, including 22,915 participants from 72 trials, revealed a RR of 0.89 (95 % CI: 0.84 to 0.95; *P*=0.0007, random effects model) in favor of corticosteroids *vs.* placebo or usual care.[80] Likewise, corticosteroids reduced 90-day mortality (13 trials, *n*=8360; RR=0.89, [95 % CI: 0.82 to 0.97]; *P*=0.01), ICU mortality (24 trials, *n*=8866; RR=0.90, [95 % CI: 0.83 to 0.98], *P*=0.01), and hospital mortality (40 trials, 17,459 participants; RR=0.90, 95 % CI: 0.84 to 0.97; *P*=0.004). The effects of corticosteroids on long-term mortality were less certain (12 trials, 8468 participants; RR=0.97, 95% CI: 0.91 to 1.03; *P*=0.27). A retrospective analysis of stepwise change in hydrocortisone administration and 90-day mortality, using data from the ADRENAL trial,[79] found an increase in the use of hydrocortisone therapy from 28 % to 43 % (*P* <0.0001) and a decrease in 90-day mortality (14 % *vs.* 24 %, adjusted hazard ratio for hydrocortisone effect 0.81; 95 % CI: 0.65 to 0.99; *P*=0.044).[90] Another real-life analysis of the use of corticosteroids found that, in norepinephrine-treated septic shock, treatment with hydrocortisone plus fludrocortisone resulted in a significant −3 % absolute reduction in mortality relative to administration of hydrocortisone alone,[91] consistent with the findings of the Corticosteroids and Intensive Insulin Therapy for Septic Shock (COIITSS) trial.[92]

Corticosteroids have uncertain effects on long-term cognitive dysfunction and mental health

It has been reported that treatment with high concentrations of glucocorticoids may alter hippocampus and prefrontal cortex function, with subsequent impairment of memory and cognitive function.[93] Nevertheless, glucocorticoids may prevent post-traumatic stress disorders.[93] Future studies should prospectively assess the long-term effects of hydrocortisone and/or fludrocortisone on cognitive function and mental health.

Corticosteroid-associated complications in sepsis

A meta-analysis of 47 trials (*n*=13,893 participants) specifically addressed the issue of serious short-term complications of corticotherapy for sepsis, community-acquired pneumonia, and acute respiratory distress syndrome (ARDS).[94] The study found, with moderate certainty, that corticosteroids did not increase the risk of gastroduodenal bleeding (relative risk=1.08, 95 % CI: 0.87 to 1.34) or of superinfections (relative risk=0.97, 95 % CI: 0.89 to 1.05). Furthermore, the results of this meta-analysis indicated that corticosteroids may not increase the risk of muscle weakness (relative risk=1.22, 95 % CI: 1.03 to 1.45) or neuropsychiatric disorders (relative risk=1.19, 95 % CI: 0.82 to 1.74), and there was moderate to high certainty of an increased risk of hyperglycemia (relative risk=1.21, 95 % CI: 1.11 to 1.31) or hypernatremia (relative risk=1.59, 95 % CI: 1.29 to 1.96). These findings are consistent with more recent data.[80] Furthermore, use of corticosteroids during the recent coronavirus disease (COVID)-19 pandemic appears to have been associated with an increased risk of opportunistic infections (e.g., tuberculosis, fungi, *Pneumocystis jirovecii*).[95]

Use of Corticosteroids for Sepsis in Clinical Practice

The authors' preferences regarding corticosteroid use in sepsis are summarized in Figure 1.

Patient selection

The most recent guidelines suggest administering corticosteroids to adult patients: (1) with septic shock (conditional recommendation, low certainty of evidence); (2) with ARDS (conditional recommendation, moderate certainty of evidence); and (3) hospitalized with severe bacterial community-acquired pneumonia.[96] The findings of the most recent and comprehensive systematic review and meta-analysis are consistent with these recommendations.[80] Indeed, this meta-analysis found that, compared to placebo or usual care, corticosteroids likely reduce 28-day mortality (RR=0.89, 95 % CI: 0.84 to 0.95; 72 trials, *n*=22,915; moderate-certainty evidence), with no evidence of differences in response to treatment between: children and adults (test for subgroup differences: χ^2=0.34, degrees of freedom [df]=1, *P*=0.56; I^2=0 %); patients with or without critical illness associated with corticosteroid insufficiency (test for subgroup differences: χ^2=0.20, df=1, *P*=0.66);

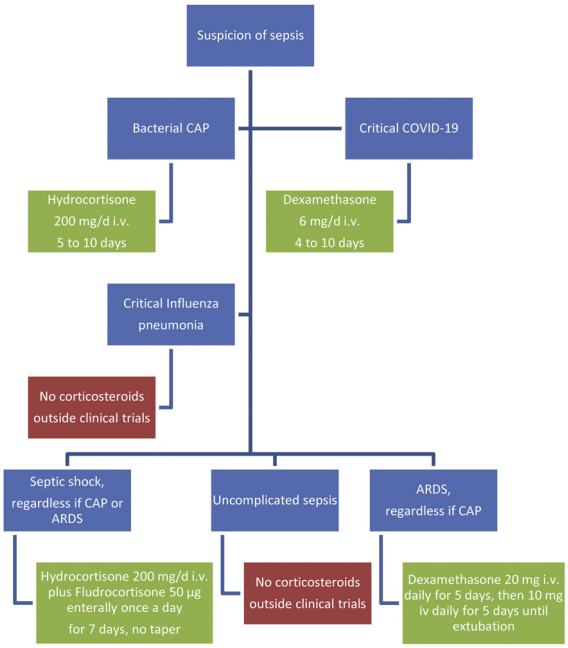

Figure 1. Decision tree for the use of corticosteroids in intensive care unit adults with sepsis.
ARDS: Acute respiratory distress syndrome; CAP: Community-acquired pneumonia; i.v.: Intravenous injection.

or patients with varying disease severity (meta-regression, P=0.5013). Nevertheless, there was evidence for significant differences in treatment response according to patient baseline phenotype (test for subgroup differences: χ^2=16.05, df=4, P=0.003; I^2=75.1 %). More specifically, in uncomplicated sepsis, corticosteroids may have no effect on 28-day mortality (RR=1.08, 95 % CI: 0.90 to 1.28; P=0.41; random-effects model; 14 studies, n=1825). Conversely, corticosteroids likely reduce 28-day mortality in patients with: septic shock (RR= 0.93, 95 % CI: 0.86 to 1.00; P=0.04; random-effects model; 29 studies, n=8871); sepsis and ARDS (RR= 0.59, 95 % CI: 0.42 to 0.83; P=0.002; random-effects model; five studies, n=496); sepsis and community-acquired pneumonia (RR=0.68, 95 % CI: 0.54 to 0.86; P=0.001; random-effects model; 16 studies, n=3818); and COVID-19-related sepsis (RR=0.88, 95 % CI: 0.81 to 0.95; P=0.002; random-effects model; seven studies, n=7764).[80] There is insufficient evidence to support the use of corticosteroids in other viral pneumonia, particularly in the treatment of influenza.[97] Ongoing studies (NCT04381936, NCT02735707) may provide more information about the benefits and harms of corticosteroids in severe influenza.

Corticosteroid regimens

For patients with septic shock, the most recent guidelines suggest continuous intravenous hydrocortisone infusion at 200 mg daily, or q6 for 7 consecutive days or up to ICU discharge, depending which occurs first.[96] There is no recommendation about the use of fludrocortisone in addition to hydrocortisone. Two trials found that a combination of hydrocortisone (50 mg intravenous bolus q6 for 7 days) with fludrocortisone (50 µg enterally once a day for 7 days) significantly reduced all-cause mortality relative to placebo.[12,77] A third trial found a –3 % absolute reduction in hospital mortality with hydrocortisone plus fludrocortisone relative to hydrocortisone alone.[92] In a retrospective study with target trial emulation, using a large healthcare US dataset, the primary composite outcome of death in hospital or discharge to hospice occurred in 1076 (47.2 %) patients treated with hydrocortisone plus fludrocortisone and 43,669 (50.8 %) treated with hydrocortisone alone (adjusted absolute risk difference of –3.7 %; 95 % CI:4.2 % to –3.1 %; P < 0.001).[91] Furthermore, a meta-analysis of individual patient data suggested that hydrocortisone plus fludrocortisone may be superior to hydrocortisone alone in adults with septic shock.[98] In addition, two trials have found that fludrocortisone given enterally to adults with septic shock is well absorbed and demonstrates reliable pharmacokinetics/pharmacodynamics in these critically ill patients.[99,100]

In community-acquired pneumonia-related sepsis, physicians may consider intravenous administration (bolus or continuous infusion) of hydrocortisone at 200 mg daily for 7 days, or for 4–8 days according to clinical improvement, and then tapering for 8–14 days, or until ICU discharge, depending on which occurs first.[96] Methylprednisolone administration is another potential option. The dosing regimen for methylprednisolone may be intravenous 0.5 mg/kg every 12 h for 7 days (within 36 h of hospital admission) or starting at 40 mg continuous intravenous infusion for 7 days, followed by tapering of the daily dose by half every week.[96] Finally, in patients with sepsis and ARDS, physicians may administer intravenous dexamethasone 20 mg daily for 5 days, then 10 mg daily for 5 days until extubation, or methylprednisolone 1 mg/kg intravenous bolus, followed by continuous intravenous perfusion of 1 mg/kg for 2 weeks, then taper the daily dose by half every week.[96]

The most recent systematic review and meta-analysis suggested that lower doses of corticosteroids given in the first 24 h, lower cumulative dose, and longer treatment duration were associated with a lower RR for dying at 28 days (P=0.03, P=0.02, and P=0.04, respectively).[80] In contrast, the study found no evidence for differences in treatment response between patients in which drug treatment was terminated compared with those in which it was tapered off. One study including a crossover trial highlighted that, in patients with septic shock, premature termination (before 72 h) of hydrocortisone was associated with a rebound in excessive inflammation and recurrence of shock.[87]

Future Challenges

Information about the benefits and risks of corticosteroids in children remains insufficient, while ongoing trials may inform future clinical practice (Table 2). The optimal dosing regimens for corticosteroids in patients with different clinical phenotypes require clarification; in particular, whether fludrocortisone provides added value warrants further investigation. The early identification of patients with a high probability of benefiting from corticosteroids *vs.* those more likely to be harmed by these drugs is among the top priorities currently under investigation by several groups (Table 2). Several candidate markers for harms or benefits from corticosteroids have been identified in the past two decades, including: endocrine markers based on steroid hormone response to adrenocorticotropic hormone tests,[77,101] serum levels of cytokines/chemokines,[102] intelligent algorithms,[103,104] and transcriptome signatures.[105,106]

Table 2
Ongoing trials evaluating the use of corticosteroids in sepsis.

Registration number/acronym	Population	Design	Corticosteroid dosing regimen	Primary outcome	Country	Sponsor
NCT05334316	Adults with pneumonia without shock *n*=24	Phase 2 Open-label randomized trial on 2 parallel groups	Dexamethasone *vs.* usual care	Adherence to individual treatment rule and CRP-guided corticosteroid treatment	USA	Mayo Clinic
NCT05354778 HYDRO-SHIP	Adults with healthcare or ventilator-associated pneumonia without shock *n*=180	Placebo-controlled randomized trial on 2 parallel groups	Hydrocortisone (100 mg q8 for 5 days) *vs.* placebo	Composite outcome: Death OR Respiratory worsening OR Cardiovascular worsening	Brazil	Instituto de Assistencia Medica ao Servidor Publico Estadual
NCT02735707 REMAPCap	Children and adults with CAP of sufficient severity to require ICU admission and associated with substantial mortality *n*=20,000	Multifactorial Adaptive Platform Trial, open label	Shock-dependent hydrocortisone (200 mg daily) OR Fixed-duration dexamethasone *vs.* usual care	90-day all-cause mortality	Multinational	UMC Utrecht
NCT03401398 SHIPSS	Children (1 month to 17 years and 8 months old) with septic shock *n*=500	Phase 3, randomized, placebo-controlled trial on 2 parallel groups	Hydrocortisone initial bolus of 2 mg/kg intravenous (maximum 100 mg), followed by 1 mg/kg (maximum 50 mg) q6 for a maximum of 7 days or until all vasoactive infusions have been discontinued for >12 h *vs.* placebo	New or progressive multiple organ dysfunction syndrome as assessed using the Pediatric Logistic Organ Dysfunction (PELOD-2) instrument	Multinational	Seattle Children's Hospital
NCT04280497 RECORDS	Adults with sepsis, septic shock, CAP or sepsis and ARDS, and having at least one measured biomarker to guide corticosteroids *n*=capped at 1800	Phase 3, Bayesian adaptive, Basket trial, placebo-controlled trial on multiple parallel arms	Hydrocortisone as 50 mg intravenous bolus q6 for 7 days plus fludrocortisone 50 μg enterally once a day for 7 days	90-day mortality and Persistent organ dysfunction (continued dependency on mechanical ventilation, renal replacement therapy, or vasopressors) and with SOFA score ≤6 up to 90 days	Multination in France	Assistance Publique Hôpitaux de Paris

ARDS: Acute respiratory distress syndrome; CAP: Community-acquired pneumonia; CRP: C-reactive protein; ICU: Intensive care unit; SOFA: Sequential organ failure assessment.

In summary, the use of supraphysiologic doses of corticosteroids for a week or two in patients with sepsis is supported by biological and pharmacological rationale, evidence from clinical trials, and high-quality systematic reviews and meta-analyses, as well as clinical practice guidelines.

CRediT Authorship Contribution Statement

Jihene Mahmoud: Writing – original draft, Conceptualization. **Marie Alice Bovy:** Writing – original draft, Conceptualization. **Nicholas Heming:** Writing – review & editing, Conceptualization. **Djillali Annane:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

Not applicable.

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