Adrenal function and dysfunction in critically ill patients

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Abstract | Critical illnesses are characterized by increased systemic cortisol availability, which is a vital part of the stress response. Relative adrenal failure (later termed critical-illness-related corticosteroid insufficiency (CIRCI)) is a condition in which the systemic availability of cortisol is assumed to be insufficiently high to face the stress of the illness and is most typically thought to occur in the acute phase of septic shock. Researchers suggested that CIRCI could be diagnosed by a suppressed incremental cortisol response to an injection of adrenocorticotropic hormone, irrespective of the baseline plasma cortisol. This concept triggered several randomized clinical trials on the impact of large stress doses of hydrocortisone to treat CIRCI, which gave conflicting results. Recent novel insights into the response of the hypothalamic–pituitary–adrenal axis to acute and prolonged critical illnesses challenge the concept of CIRCI, as currently defined, as well as the current practice guidelines for diagnosis and treatment. In this Review, these novel insights are integrated within a novel conceptual framework that can be used to re-appreciate adrenocortical function and dysfunction in the context of critical illness. This framework opens new avenues for further research and for preventive and/or therapeutic innovations.

Critical illness
Any trauma or disease leading to life-threatening organ dysfunction that requires mechanical or pharmacological support to prevent imminent death.

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Critical illness causes severe physical stress to which the body must respond in order to restore homeostasis[1]. The hypothalamus, pituitary and adrenal glands, which form the hypothalamic–pituitary–adrenal (HPA) axis, have a central, orchestrating role in the stress response[2–4]. In critically ill patients, stressors comprise a variety of neuronal and inflammatory signals that directly or indirectly act on the hypothalamic nucleus paraventricularis to stimulate the synthesis and secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). Subsequently, the hypophyseal portal circulation transports CRH and AVP from the hypothalamus to the anterior pituitary gland, where these hormones trigger corticotrope cells to release adrenocorticotropic hormone (ACTH) into the systemic circulation.

Once in the zona fasciculata of the adrenal cortex, ACTH activates key enzymes required for steroidogenesis and cortisol release. Consequently, increased circulating levels of cortisol exert systemic effects in almost every cell type via genomic (through binding with the glucocorticoid receptor) and non-genomic effects. In addition to modulating inflammation, cardiovascular function and metabolism, cortisol regulates its own production by binding to the glucocorticoid receptor in the hypothalamus and the pituitary, which decreases ACTH secretion via short and long feedback loops to regain homeostasis.

A state of centrally activated hypercortisolism is considered to be the cornerstone of the human endocrine stress response. Within this paradigm, until 2013, intensive care physicians considered the several-fold-higher circulating cortisol levels in critically ill patients to be the net result of a 6–10-fold increased rate in cortisol production, which was driven by increased synthesis of CRH, AVP and ACTH[5,6]. However, over the past years, it has become clear that high circulating cortisol levels in critically ill patients do not coincide with high ACTH plasma concentrations. This so-called ACTH-cortisol dissociation has recently been further scrutinized[7–12]. The results of this research have generated a shift in the paradigm of the adrenocortical stress response to critical illness.

In this Review, we highlight newly generated insights into the responses of the HPA axis to critical illness and integrate them into a novel conceptual framework that can be used to reassess adrenocortical function and dysfunction in this context (FIG. 1). Although this framework remains an oversimplification, it may provide a new basis with which to reconsider current practice guidelines for the diagnosis and treatment of what is referred to as critical-illness-related corticosteroid insufficiency (CIRCI)[13,14].

The stress response to critical illness

The normal response to psychological distress, physical strain, tissue damage or infection comprises a rise in systemic cortisol availability, which is evidenced by increased plasma concentrations of total cortisol and

Key points

- The amount of cortisol that is produced by patients during critical illness is not much higher, if at all, than that produced when healthy.
- Increased systemic cortisol availability during critical illness is largely driven by decreased cortisol-binding proteins in the circulation, by the reduced binding affinity of these proteins and by suppressed cortisol breakdown.
- Circulating free cortisol that is elevated via such peripheral mechanisms may partially explain why adrenocorticotropic hormone (ACTH) levels are low in patients with critical illness, owing to feedback inhibition.
- Low ACTH levels that are present for an extended period of time may negatively affect adrenocortical integrity and function.
- An ACTH stimulation test is invalid for assessing adrenocortical integrity and function in critically ill patients, as the test results are confounded by the increased cortisol distribution volume.
- Doses of hydrocortisone currently advised for treating critically ill patients do not take the substantially increased half-life of cortisol into account, are thus likely too high and may further increase central adrenocortical suppression via feedback inhibition.
- Future research should focus on patients who are critically ill for an extended period, on patients who may be at risk of developing central hypoadrenalism and on novel strategies to prevent and treat this complication.

free (non-protein-bound) cortisol (FIG. 2). In critically ill patients treated in the intensive care unit (ICU), the severity of the traumatic stress or infectious insult is positively correlated with the degree of hypercortisolism[15–18]. This association is likely an evolutionary conserved beneficial adaptation, given that cortisol has profound metabolic, cardiovascular and immunological effects, which are required for an adequate fight-or-flight reaction.

Cortisol suppresses anabolism and stimulates catabolism, thereby ensuring provision of sufficient elementary sources of energy during times of stress[19,20]. Moreover, cortisol causes fluid retention via activation of the mineralocorticoid receptor and increases myocardial contractility and blood pressure via the potentiation of catecholamine effects in cardiovascular smooth muscle cells[21,22]. In addition, cortisol regulates the innate immune response and inflammation[23]. Cortisol has both immune-stimulatory and immune-suppressive or anti-inflammatory effects; these effects follow a bi-phasic dose–response curve. Consequently, low concentrations of cortisol exert immune-stimulatory effects, and high concentrations of cortisol induce immune-suppressive effects[23]. Basal levels of cortisol can sensitize cells to harmful stimuli even in the absence of inflammation by increasing the expression of cytokine receptors, pattern recognition receptors and complement factors. These proteins are innate immune components that enable the rapid detection of pathogen-associated molecular patterns and damage-associated molecular patterns and facilitate the induction of inflammation in response to tissue damage or infection. If higher concentrations of cortisol are encountered under inflammatory conditions, the immune response will become suppressed; this response occurs primarily by a decrease in the expression of pattern recognition receptors and Fc receptors and a decrease in cytokine signalling[23]. In critically ill patients, the consequences of increased systemic cortisol availability are considered to be vital in order to avoid shock and organ failure, to combat infections and to repair tissue damage, which all facilitate recovery. Interestingly, very high levels and very low levels of circulating cortisol have been associated with poor outcomes in critical illnesses[24,25], indicating the importance of a well-balanced, adequately timed, bi-phasic and dose-dependent cortisol response for survival.

Synthesis and secretion of cortisol during critical illness. On the basis of the classical concept of the HPA stress response, one would assume that trauma or severe illness would induce a rapid rise in plasma concentrations of ACTH and cortisol, sustained sufficiently long enough to bridge to recovery. Indeed, a few small studies of patients undergoing surgery reported high plasma concentrations of ACTH and cortisol during surgery and at the end of surgery[26,27]. However, in the hours after surgery, plasma ACTH concentrations rapidly decreased, whereas plasma cortisol remained elevated[27,28]. Studies have also reported total plasma cortisol that rose only hours after the end of surgery[10,28]. On the assumption that critical illness that necessitates vital organ support represents a condition of severe physical and inflammatory stress, one would expect a rapid and very pronounced rise in plasma ACTH and cortisol in patients admitted to the ICU, which would provide evidence for the presumed several-fold increased ACTH-driven cortisol production rate[29,30]. Quite surprisingly, however, one 1995 study documented only transiently increased plasma ACTH levels in patients with sepsis or who had experienced major trauma, whereas plasma cortisol levels remained higher than normal levels for at least 7 days[31] (BOX 1). More recently, a 2013 report documented that in a mixed population of patients admitted to a tertiary ICU, from day 1 after admission and throughout the first week, plasma ACTH levels were low rather than high. Furthermore, low ACTH levels were always accompanied by elevated plasma total cortisol and free cortisol levels[7] (FIG. 2). These findings are not quite compatible with the hypothesis of ongoing ACTH-driven increased production of cortisol during critical illness[7,31].

A model of ACTH-independent, inflammation-driven cortisol production that feeds into the HPA axis was suggested by studies demonstrating that direct ligation of Toll-like receptor 2 (TLR2) and TLR4 in adrenocortical cells activates cortisol production[32]. However, a 2013 stable isotope tracer study (using deuterated cortisol) of patients in the ICU reported that the cortisol production rate of patients was either not increased or was less than twice that of healthy matched volunteers, even in the face of several-fold-higher total cortisol and free plasma cortisol concentrations[7]. The moderate increase in cortisol production that was documented only in critically ill patients with hyperinflammation could indeed be explained by infection or inflammation[33]. In addition to the presence of pathogens, other causes of tissue damage, such as burn injury, multiple trauma or complicated surgery, might lead to the systemic release of the vasoconstrictor endothelin, which is considered to be another direct driver of inflammation-driven cortisol production[31].

Most studies reporting plasma concentrations of cortisol and/or ACTH during critical illness have taken, at

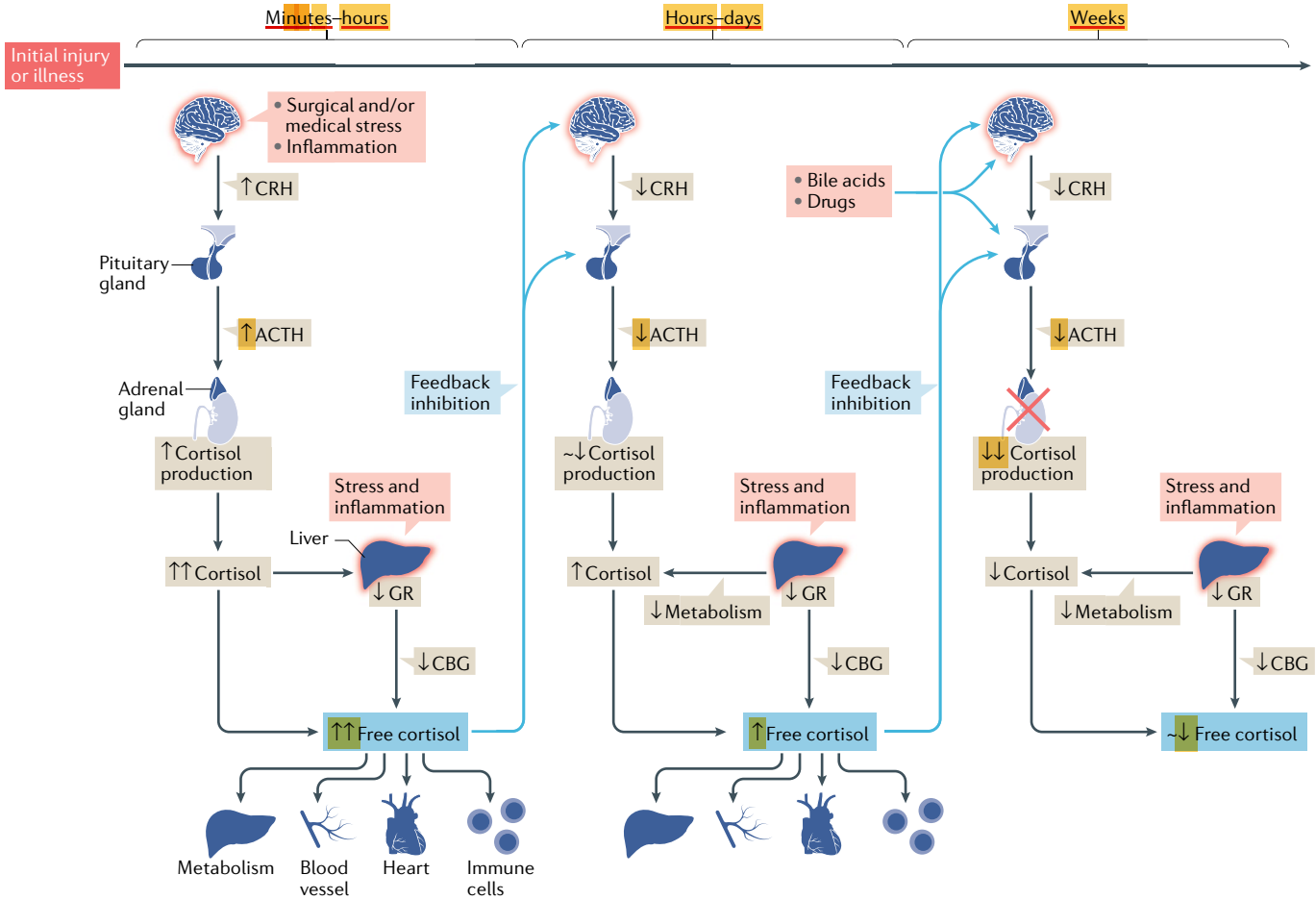

Fig. 1 | **Newly proposed conceptual framework for adrenocortical function and dysfunction during critical illness.** The mechanisms behind the alterations to the hypothalamic–pituitary–adrenal (HPA) axis during critical illness are depicted, integrating central and peripheral drivers of increased cortisol availability during the acute, sub-acute and chronic phases of critical illness. The acute phase (occurring within minutes to hours after the initial insult) is mostly characterized by a central, adrenocorticotropic hormone (ACTH)-driven rise in cortisol and a peripherally driven (by decreases in cortisol binding to cortisol-binding proteins, in addition to glucocorticoid receptor (GR)-driven effects) further rise in free cortisol. By contrast, the sub-acute phase (occurring hours to days after initial insult) is marked by central suppression driven by feedback inhibition with sustained peripherally driven elevated total cortisol and free cortisol. During the chronic phase, extending beyond several weeks of critical illness, the sustained central suppression of the HPA caused by feedback inhibition driven by sustained elevation of free cortisol and by elevated bile acids and/or drugs could lead to central hypoadrenalism. CBG, cortisol-binding globulin; CRH, corticotropin-releasing hormone.

best, one hormone measurement per day[34,35]. However, the secretion of ACTH and cortisol into the systemic circulation occurs in a pulsatile fashion, which is superimposed over a non-pulsatile, basal level of secretion[36]. Quantification of the hormone secretion rate from a plasma concentration requires time series with frequent sampling, preferably at least every 10 minutes, followed by deconvolution analysis that takes the plasma half-life of the hormone into account[36]. In a 2014 study, overnight ACTH and cortisol secretion rates were deconvolved from plasma concentration time series obtained from critically ill patients and matched healthy volunteers[8]. Notably, this study showed that the nocturnal pulsatile secretion rate of both ACTH and cortisol was lower in patients than in healthy subjects, although not totally suppressed, owing to smaller hormone pulses released in the patients at a normal pulse frequency. In addition, the dose–response relationship between ACTH and cortisol secretion was normal throughout the first 10 days or so of illness, indicating that feedback inhibition plays a homeostatic role.

Elevated free cortisol via reduced plasma binding. Systemic cortisol availability during critical illness is many-fold increased, although this effect is apparently not brought about by increased ACTH-driven cortisol secretion[7–9]. A striking change that explains at least part of this phenomenon is a pronounced decrease in the levels of plasma cortisol-binding proteins and a reduction in their binding affinity[37,38]. During health, ~90% of circulating cortisol is bound to a carrier protein, with 80% bound to cortisol-binding globulin (CBG) and 10% bound to albumin. Only the 10% unbound 'free' cortisol fraction is lipid soluble and can diffuse across the cell membrane to bind to the cytoplasmic glucocorticoid receptor. Free cortisol is difficult to quantify in plasma,

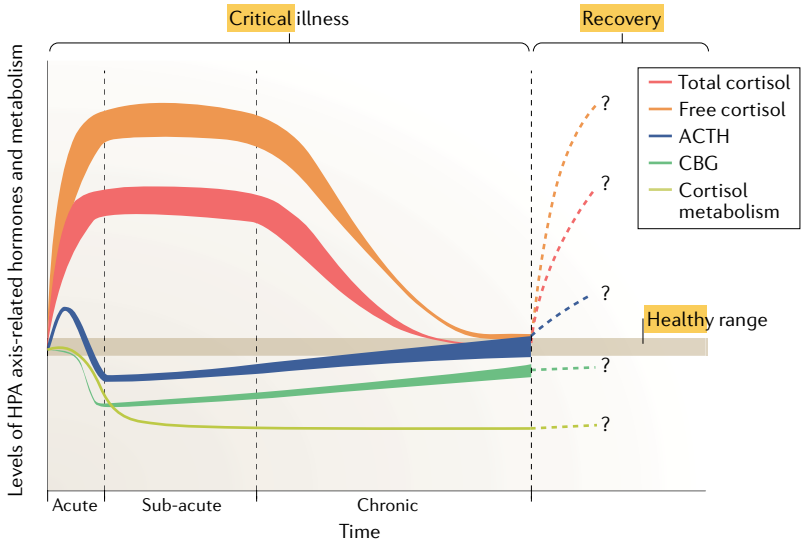

Fig. 2 | **Time-dependent and dose-dependent changes in plasma concentrations of key components during critical illness.** The graph shows the dynamic alterations in the plasma concentrations of adrenocorticotropic hormone (ACTH), total cortisol, cortisol-binding globulin (CBG) and free cortisol and in cortisol metabolism following the onset of critical illness. The acute phase is mostly characterized by a centrally ACTH-driven rise in cortisol; the sub-acute phase is marked by sustained elevated total cortisol and free cortisol but low plasma ACTH levels; the chronic phase is a phase during which neither plasma ACTH nor plasma cortisol levels are elevated above normal; and the recovery phase is that in which plasma ACTH and (free) cortisol rise to supra-normal levels that often exceed those present during critical illness. Whether and when the plasma concentrations return to normal values remain unclear.

although it can be reliably estimated in the context of health and critical illness, with use of the (modified) Coolens formula, which is based on total plasma cortisol, plasma CBG and plasma albumin concentrations[39–41].

Circulating CBG and albumin decrease rapidly and substantially in critically ill patients (FIG. 2). The causes of low albumin levels comprise losses via bleeding or enteropathy, capillary leakage of albumin into the interstitial space and dilution due to fluid resuscitation[42,43]. Whether or not albumin synthesis is actually decreased during critical illness remains unclear[44,45].

The circulating levels of CBG rapidly drop within hours after the onset of illness and remain low throughout ICU stay[10,11,46]. Research from 1997 suggested that pro-inflammatory cytokines suppressed CBG synthesis in the liver[47]. However, a 2018 study further scrutinized the mechanism behind the rapid decrease in CBG in critical illness[48]. In a clinically relevant mouse model of sepsis, low levels of CBG could be partially attributed to downregulation of the hepatic glucocorticoid receptor. The presence of sepsis suppressed the expression of the hepatic glucocorticoid receptor as well as signalling, possibly via cytokines or via the initially increased binding of cortisol to the hepatic glucocorticoid receptor; this reduction in turn led to decreases in CBG, therefore increasing the circulating free corticosterone, which is the main glucocorticoid in rodents (FIG. 1). Indeed, a decrease in CBG leads to a rise in free cortisol or corticosterone, which may occur even without alterations in total cortisol or corticosterone concentrations[49]. Interestingly, in this mouse study, elevated free corticosterone levels were associated with low levels of ACTH through a mechanism of negative-feedback inhibition[48].

In addition to low circulating levels of CBG, neutrophil elastase proteolytically cleaves CBG, which causes the loss of its high-affinity binding potential with cortisol[38]. Furthermore, in critically ill patients, low blood pH and high blood temperature may contribute to decreased binding affinity between CBG and cortisol[37,50]. The decrease in high-affinity CBG has shown to be proportionate to the severity of shock[46].

Decreased cortisol metabolism. Cortisol is broken down enzymatically predominantly in the kidneys and liver, and decreased cortisol metabolism is a second peripheral driver of increased systemic cortisol availability during critical illness. One metabolic pathway is the reversible oxidation of active cortisol into inactive cortisone via 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2. Whereas 11β-HSD type 2 is predominantly expressed in the kidney, the other isoform, 11β-HSD type 1, is expressed in various cortisol target tissues, such as the liver, heart, blood vessels, adipose tissue and immune cells[51]. 11β-HSD type 1 primarily reduces cortisone to cortisol, thereby opposing the effects of 11β-HSD type 2 (REF.[52]). Another metabolic pathway can be considered the principal route of irreversible cortisol breakdown: two A-ring reductase enzymes, 5α-reductase and 5β-reductase, degrade cortisol (both enzymes) and cortisone (only 5β-reductase) into di-hydro-metabolites, which are further reduced to tetra-hydro-metabolites[53]. Both 5α-reductases and 5β-reductases are predominantly, but not exclusively, expressed in the liver. Cortisol, cortisone and their metabolites are excreted via the urine. In conclusion, the regulation of cortisol metabolism is complex and multifactorial[54].

In 2013, a mixed cohort study of critically ill patients matched with healthy volunteers showed that the activity of the main cortisol-metabolizing enzymes, 5α-reductase, 5β-reductase and 11β-HSD type 2, was decreased in critical illness[7]. This study was evidenced by enzyme activity estimations obtained through quantification of urinary metabolites and via stable isotope studies. Furthermore, in liver biopsy samples obtained post-mortem from critically ill patients, A-ring reductase mRNA and protein expression was substantially suppressed[7]. Thus, hypercortisolaemia in critically ill patients is, to a large extent, explained by decreased cortisol plasma clearance, which occurs via suppressed expression and activity of the cortisol-metabolizing enzymes (FIGS. 1, 2). Interestingly, the cortisol production rate was only slightly increased in patients with hyperinflammation (BOX 1), suggesting a moderate direct stimulation of the adrenal cortex, whereas cortisol clearance was uniformly reduced in all critically ill patients, irrespective of type and duration of illness[7,11].

The role of bile acids and the hepatic glucocorticoid receptor. In addition to their function in facilitating lipid and cholesterol absorption and distribution, bile acids are increasingly recognized as regulators of endocrine homeostasis and inflammation. The discovery of

Fluid resuscitation
The administration of intravenous fluids during the first hours after onset of sepsis with the aim to stabilize and/or reverse sepsis-induced tissue hypoperfusion and prevent evolution to septic shock.

Neutrophil elastase
A serine protease that is secreted by immune cells, such as activated neutrophils, during inflammation. This enzyme hydrolyses a broad range of proteins, including cortisol-binding globulin (CBG).

two bile acid receptors, the nuclear farnesoid X receptor (also known as the bile acid receptor) and the G protein-coupled bile acid receptor 1, has led to important insights into the effects of bile acids in inflammation-driven diseases, with implications for sepsis and other critical illnesses[55–57]. Bile acids are synthesized from cholesterol, which is also the precursor molecule for cortisol. Moreover, several enzymes involved in the complex regulation of cortisol metabolism are involved in the regulation of bile acids. Importantly, 5β-reductase, the major cortisol-metabolizing enzyme, is also essential for bile acid synthesis[58]. Via negative-feedback loops, bile acids suppress 5β-reductase expression and activity to decrease bile acid production, thereby simultaneously reducing cortisol breakdown by 5β-reductase. In vivo, this effect has been shown in animal models and in patients with cholestatic liver diseases[59,60]. A 2013 study showed that in critically ill patients, circulating levels of bile acids are elevated and inversely correlate with the hepatic expression of 5β-reductase and positively correlate with plasma cortisol levels[7]. Thus, the elevation of intrahepatic levels and circulating levels of bile acids that occurs in response to critical illness may possibly contribute to the inhibition of cortisol breakdown. Consequently, the rise in circulating bile acids in response to critical illness may not necessarily reflect cholestasis as a pathophysiological entity but could be a marker and/or mediator of the endocrine adaptive stress response[61].

Interestingly, two studies showed that, specifically, the hepatic glucocorticoid receptor modulates the availability of bile acids via regulating the expression of A-ring reductases[62,63]. Moreover, selective suppression of the hepatic glucocorticoid receptor via small interfering RNAs in a mouse model of sepsis-induced critical illness has been shown to prevent the acute sepsis-induced rise in bile acids, although this effect was transient[48]. By contrast, selective suppression of the hepatic glucocorticoid receptor further accentuated the sepsis-induced downregulation of the A-ring reductases in the liver[48]. Thus, sepsis-induced hepatic glucocorticoid receptor suppression seems to partly explain the suppression of cortisol breakdown, but other drivers besides bile acids are probably also involved. Further suppression of the hepatic glucocorticoid receptor in a mouse model of sepsis also resulted in potentially lethal liver and systemic inflammation, irrespective of corticosterone availability[48]. Together, these data indicate that a fine-tuned regulation of glucocorticoid receptor expression and activity in the liver is key in controlling both the HPA response and the inflammatory responses to critical illnesses[48].

Regulation of glucocorticoid receptor expression in critical illness. The glucocorticoid receptor is encoded by *NR3C1*, which has at least two major splice variants that can be found in nearly all nucleated cells[64]. The dominant functional receptor is the glucocorticoid receptor-α isoform, whereas the glucocorticoid receptor-β variant, which is expressed at far lower levels than the glucocorticoid receptor-α in healthy individuals, is dominant-negative. Before ligand binding, the glucocorticoid receptor resides in the cytoplasm as part of a multimeric complex. Upon binding with cortisol, the multimeric complex dissociates, with uncoupling of the chaperones heat shock protein 70 (HSP70) family, HSP90 and FKBP51 (also known as PPIase FKBP5)[65,66]. The newly formed cortisol–glucocorticoid receptor complex translocates to the nucleus, where it can induce expression of, or repress up to 20% of, the genome[67,68]. Three major mechanisms exist that can exert these genomic effects. First, glucocorticoid receptor dimers can bind directly with genomic glucocorticoid response elements (GREs) and affect gene expression[69]. As such, the cortisol–glucocorticoid receptor complex serves as a transcription factor. A second mechanism is the binding of cortisol–glucocorticoid receptor with another transcription factor to alter the transcriptional capacity of said transcription factor. In this model, the glucocorticoid receptor does not make direct contact with the DNA strand; the protein–protein binding is often referred to as tethering[23,70]. A third mechanism is the binding of cortisol–glucocorticoid receptor directly to a DNA section that contains both a GRE and a response element for another transcription factor[71].

In addition to the genomic effects mediated via the glucocorticoid receptor, cortisol has some glucocorticoid receptor-independent effects that are mediated via the intercalation of cortisol in the cell membrane or in mitochondrial membranes, which subsequently leads to altered transmembrane ion transport[72]. These non-genomic effects of cortisol occur within seconds to minutes, in contrast to the genomic effects of the cortisol–glucocorticoid receptor complex, which typically take hours or days to occur. Current thinking is that the immunosuppressive and anti-inflammatory effects of glucocorticoids are brought about by the mechanism of tethering and that the other effects of glucocorticoids are brought about by direct transcriptional activity at the GREs, although this model is likely an oversimplification of the complex set of genomic and non-genomic mechanisms[23].

In addition to the important role of a fine regulation of hepatic glucocorticoid receptor expression in response to sepsis-induced critical illness, data from a 2018 study suggest that in other cell types, such as immune cells and cells of the cardio-respiratory system, sepsis may evoke

Box 1 | **Commonly used intensive care unit-related terms and definitions**

- Hyperinflammation: this is an updated term for the state of inflammation in critically ill patients that was previously defined by the systemic inflammatory response syndrome criteria[128].
- Sepsis[a]: this is defined as life-threatening organ dysfunction, which is caused by a dysregulated host immune response to infection. Sepsis is diagnosed when a patient has an increase in the sequential (sepsis-related) organ failure assessment[129] score of >2 points; such an increase is associated with an in-hospital mortality of >10%.
- Septic shock[a]: this is defined as a condition that develops in patients with sepsis, in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of death than that from sepsis alone. Septic shock is present when there is a vasopressor requirement to maintain a mean arterial pressure of ≥65 mmHg and serum lactate level of >2 mmol/l (>18 mg/dl) in the absence of hypovolaemia. Septic shock is associated with an in-hospital mortality of >10%.

[a]Definitions of both sepsis and septic shock were updated in 2016 in the 'The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)'[130].

Glucocorticoid resistance
A decrease in the cellular response to endogenous or exogenous glucocorticoids.

Waterhouse–Friderichsen syndrome
A life-threatening acute adrenal haemorrhage that leads to adrenal failure, which is caused by severe bacterial infections, most often involving meningococci or streptococci.

a shift in glucocorticoid receptor expression, from the glucocorticoid receptor-α isoform to the glucocorticoid receptor-β isoform[73,74]. Such alterations in glucocorticoid receptor isoform expression could contribute to the so-called glucocorticoid resistance in sepsis[73,75]. However, another study reported an upregulation of the glucocorticoid receptor-α in sepsis[76]. Whether sepsis alters other parts of the genomic and non-genomic pathways of cortisol signalling remains unclear.

The role of ACTH in critical illness

The remarkable coincidence of high plasma cortisol concentrations and low plasma ACTH levels in response to most types of critical illnesses[7,11,31], initially referred to as ACTH-cortisol dissociation, has recently triggered further research on why and how this may be happening. A study that quantified secretion rates for ACTH and cortisol, rather than plasma concentrations obtained from single samples, suggested that the term ACTH-cortisol dissociation may not be correct[8]. As mentioned above, this study showed that the overnight pulsatile secretion of ACTH and cortisol was lower in critically ill patients with elevated plasma cortisol than in healthy controls, but the dose–response of cortisol production in response to ACTH was normal in patients[8]. These data suggested that nocturnal ACTH secretion does drive nocturnal cortisol secretion but that both are suppressed during critical illness (FIG. 1). This finding could be associated with feedback inhibition exerted by circulating cortisol that is elevated via peripheral drivers, as explained above, or via other central suppressors of CRH, AVP and/or ACTH[10,11].

A large 2018 study of 347 critically ill patients requiring intensive care for at least a week showed that sustained suppression of ACTH was associated with a lack of hypercortisolism beyond 4 weeks, which is compatible with a form of central adrenocortical suppression[11]. Interestingly, when investigated again one week after ICU discharge, plasma ACTH and plasma total cortisol and free cortisol levels had increased substantially and reached levels that were much higher than those in healthy individuals. The latter finding suggests that the central adrenocortical suppression, present while patients were critically ill in the ICU, was no longer present one week later, and the hypercortisolism occurring upon recovery was more pronounced than that observed in the ICU[11]. The causes of central adrenocortical suppression could be both iatrogenic and endogenous[10,11,77]. A speculative endogenous cause, which requires further investigation, is the rise in plasma bile acids seen in critically ill patients. After passing the blood–brain barrier, bile acids can enter neurons via the apical sodium-dependent bile acid transporter (ASBT) and bind to the cytoplasmic glucocorticoid receptor[78,79]. Such binding of bile acids to the glucocorticoid receptor in hypothalamic CRH-secreting neurons can thereby cause a central HPA suppression (FIG. 1). A 2018 study has shown that beyond the first week of critical illness, the response of ACTH to a 100 µg CRH bolus injection is suppressed, which is compatible with glucocorticoid receptor-ligand binding-induced central suppression of the HPA axis[12]. This finding is again in line with feedback inhibition through peripherally driven increased cortisol availability and/or with increased glucocorticoid receptor ligands such as bile acids. This finding also does not support the hypothesis of shock-induced structural damage to cells within the hypothalamus, unlike what has been previously suggested[80,81].

Damage to the HPA axis

Structural damage to the HPA axis as the cause of critical illness. Evidently, pre-existing or de novo structural damage to the HPA axis can be a reason for admission to the ICU. Hypothalamic and pituitary diseases leading to tertiary or secondary adrenal insufficiency, though uncommon in the general population, indeed represent life-threatening conditions[82]. Even more uncommon is primary adrenal insufficiency caused by structural damage to the adrenal gland (known as Addison disease)[83], which has a prevalence of 0.03–0.05% in the Western population[84–86]. In this context, primary, secondary or tertiary adrenal insufficiency may also be referred to as absolute (see below). With an estimated population prevalence between 1% and 3%, the most common premorbid suppression of the HPA axis is long-term treatment with corticosteroids for various chronic inflammatory or neurological diseases[87]. All patients with premorbid HPA axis suppression require immediate medical attention and appropriate hormonal substitution to avoid excess morbidity and mortality evoked by critical illnesses[34,88].

Another minority population of critically ill patients will develop structural damage of the hypothalamus, pituitary or adrenal cortex because of the primary insult for which they were admitted to the hospital. Sepsis associated with disseminated fungal infections[89], tuberculosis[90] meningococcal or streptococcal Waterhouse–Friderichsen syndrome[91,92] can cause direct damage to the adrenal cortex. The exact mechanism of the adrenal haemorrhagic infarction in Waterhouse–Friderichsen syndrome is still not fully understood. Other causes of ICU-related primary and secondary adrenal insufficiency are infiltrative processes, surgery, irradiation and trauma[82]. Traumatic brain injury represents up to 20–30% of the cases with hormonal dysfunction involving the somatotropic, gonadotropic and HPA axes[93,94]. ACTH deficiency, causing central adrenal insufficiency, is also seen in one in eight patients with acute central nervous system infections such as bacterial or tuberculous meningitis[95]. Ischaemia and necrosis of the pituitary gland can also be caused by excessive blood loss, as seen in postpartum Sheehan syndrome[82]. Although rare, such a condition may lead to severe hypopituitarism, causing impaired hormonal stress responses.

Drug-induced interference with the HPA axis during critical illness. Critically ill patients require vital organ support, and one of the main strategies to deliver such support is a broad spectrum of pharmaceutical agents, including antibiotics, anti-mycotics, inotropes, anaesthetics and analgesics. However, many of these drugs have off-target adverse effects. In the 1980s, the use of etomidate as a sedative increased exponentially

because of its excellent haemodynamic properties[96]. Thereafter, studies reported lowered plasma cortisol levels and increased mortality in patients sedated with etomidate[97], an effect associated with the fact that etomidate is a potent inhibitor of 11β-hydroxylase, a key enzyme for steroidogenesis[98]. Other well-known inhibitors of adrenocortical steroidogenesis are the anti-fungal azole derivates[99]. In particular, ketoconazole inhibits 11β-hydroxylase, with a similar mechanism to but less potently than etomidate[100]. Several other pharmaceutical agents administered to ICU patients have been identified as inhibitors or, more rarely, as stimulators of the HPA axis[10]. For example, a 2017 multivariable association study identified opioids and propofol as independently associated with lower plasma cortisol concentrations[10]. Interestingly, a direct effect of opioids on the adrenal cortex, rather than an ACTH-mediated central inhibitory effect, was suggested in this context[101].

CIRCI

Relative adrenal insufficiency. HPA axis dysfunction can be present in certain ICU patients, particularly in the sickest patients, such as those with septic shock[102–104]. The term relative adrenal insufficiency was coined to describe a maximally activated adrenal cortex that produces cortisol in large quantities, which are seemingly not large enough to deal with the severe stress of illness[24,102]. In contrast to absolute adrenal insufficiency (described earlier), relative adrenal insufficiency was considered to be possible even when plasma cortisol levels are high. In 2000, a study postulated that this condition of relative adrenal failure may be diagnosed by an ACTH stimulation test and is present when the incremental total plasma cortisol response to 250 μg of ACTH is <9 μg/dl, irrespective of the basal cortisol level[105]. Furthermore, it was hypothesized that patients with relative insufficiency would benefit from glucocorticoid treatment in a stress dose, which was assumed to be approximately 200 mg of hydrocortisone per day[18,106]. Indeed, 200 mg of hydrocortisone represents the equivalent of a 6–10-fold increased cortisol production rate, which was erroneously believed to bring about the hypercortisolism of critically ill patients[5]. If relative adrenal insufficiency did indeed reflect a maximally activated adrenal cortex, with increased cortisol production that is insufficiently high to meet the needs of critical illness, one would expect very high plasma concentrations of ACTH. However, as previously mentioned, most critically ill patients, including those with septic shock, have low plasma ACTH, which does not support this concept.

Interestingly, in 2008, the term relative adrenal insufficiency was replaced with CIRCI[107]. One of the main reasons for this was the idea that an impairment of the HPA axis during critical illness could be present at any level of the HPA axis, including the hypothalamus, the pituitary and the adrenal cortex[13]. Furthermore, it was postulated that the downregulation of glucocorticoid receptor-α and upregulation of glucocorticoid receptor-β in response to sepsis and inflammation should be interpreted as an insufficiency of the HPA axis at the peripheral level of target tissues[108–110]. Alternatively, such modulation of glucocorticoid receptor expression may also be a tissue-specific beneficial adaptation, a hypothesis that remains to be further investigated. In addition, the implications of glucocorticoid resistance during critical illness remain debated. Glucocorticoid resistance has been considered by some researchers as another good reason for treating critically ill patients with high stress doses of hydrocortisone[107], whereas other groups have interpreted this as an argument against such treatment[111]. Indeed, high doses of hydrocortisone may not work in patients when there is no active glucocorticoid receptor and may further suppress glucocorticoid receptor expression[48,112]. Moreover, in biopsy samples obtained from ICU patients, it was recently shown that hepatic glucocorticoid receptor expression is further suppressed by hydrocortisone treatment[48]. Such further suppression of hepatic glucocorticoid receptor could aggravate hepatic and systemic inflammation[48].

Treatment with hydrocortisone. The hypothesis that patients with septic shock and CIRCI would benefit from stress doses of hydrocortisone was first tested in a 2002 randomized controlled trial (RCT)[113]. Investigators added 50 μg of oral fludrocortisone to a daily dose of 200 mg of intravenous hydrocortisone to patients in the intervention arm. Several other RCTs of patients with septic shock followed; the most important ones with mortality as the primary end point are listed in TABLE 1 (REFS[113–116]). Of these, two RCTs by the same principal investigator showed that mortality was reduced in the intervention arm[113,114], whereas the results of the other two, much larger trials showed no difference in mortality[115,116]. Only the first 2002 RCT revealed that patients with a low incremental total cortisol response to 250 μg of intravenous ACTH benefited from the intervention, whereas those with a higher response could be harmed[113]. However, none of the subsequent studies could confirm this difference[115,116].

The addition of fludrocortisone to the 200 mg of hydrocortisone may explain the outcome differences of the trials; however, this hypothesis appears unlikely, as all mineralocorticoid receptors are expectedly occupied after a 200 mg dose of hydrocortisone[117,118]. Another possible explanation is the use of etomidate, which varied among the studies (TABLE 1). Furthermore, the variation in responses to hydrocortisone treatment could also be explained by the pretreatment competence of the innate immune system, which may vary among patients. Immune-competent adult patients may experience the immune-suppressive effects of high doses of hydrocortisone, as opposed to those patients who already present with a suppressed innate immunity[119]. However, this could not be confirmed in critically ill children[120]. Despite ongoing controversy, clinical practice guidelines (BOX 2) continue to advise the treatment of patients with septic shock with 200–400 mg of hydrocortisone per day because of, or irrespective of, CIRCI[121,122]. The guidelines also continue to advise using an ACTH stimulation test and to diagnose CIRCI when the incremental rise in plasma total cortisol concentration is <9 μg/dl or when a random total plasma cortisol is below 10 μg/dl, although the quality of the evidence is low[14,107].

Importantly, research in 2018 showed that the results of an ACTH stimulation test are invalid in the context of

Stress dose
The pharmacological dose of glucocorticoids that was, until recently, assumed to be necessary to meet the cortisol demands of patients with critical illnesses.

Table 1 | **Major RCTs investigating the effect of glucocorticoid treatment in critical illness**

Principal investigator, year, study acronym[a]	Number of participants; main inclusion criteria	Drug dose, posology and treatment duration; tapering	Primary outcome	Predictive value of 250 µg ACTH stimulation test result	Major secondary outcomes	Major adverse effects
Annane, 2002 (REF.[113])	299 mechanically ventilated patients with septic shock	Hydrocortisone 50 mg IV bolus every 6 h + fludrocortisone 50 µg PO every 24 h during 7 days; not tapered	28-day mortality: lower in GC group	Benefit only in non-responders (incremental cortisol <9 µg/dl), potential harm in responders	Time to shock reversal: shorter in GC group	None reported
Sprung, 2008, CORTICUS[116]	499 participants, predominantly patients with septic shock; various inclusion and exclusion criteria	Hydrocortisone 50 mg IV bolus every 6 h during 5 days; tapered over 6 days	28-day mortality: no difference	No difference between responders and non-responders	Time to shock reversal: shorter in GC group	Hyperglycaemia, hypernatraemia and superinfections (new sepsis and new septic shock): more in GC group
Annane, 2018, APROCCHSS[114]	1,241 patients with probable or proven septic shock; various inclusion and exclusion criteria	Hydrocortisone 50 mg IV bolus every 6 h + fludrocortisone 50 µg PO every 24 h during 7 days; not tapered	90-day all-cause mortality: lower in GC group	No difference between responders and non-responders	Time to shock reversal and time to weaning from mechanical ventilation: shorter in GC group	Hyperglycaemia: more in GC group
Venkatesh, 2018, ADRENAL[115]	3,658 mechanically ventilated patients with septic shock; various inclusion and exclusion criteria	Hydrocortisone 200 mg IV, continuous infusion during 7 days or shorter if earlier ICU discharge; not tapered	90-day mortality: no difference	Test not performed	Time to shock reversal and time to weaning from initial mechanical ventilation: shorter in GC group	All adverse events combined: more in GC group

ACTH, adrenocorticotropic hormone; GC, glucocorticoid treatment; ICU, intensive care unit; IV, intravenous; PO, per os (oral administration); RCT, randomized clinical trial. [a]All trials in the table are multicentre, placebo-controlled, randomized, double-blind trials.

critical illness[11], because ACTH stimulation test results in this condition are flawed by the uniformly increased cortisol distribution volume in critical illness. Indeed, critically ill patients have a 40% increased cortisol distribution volume compared with that of healthy individuals, which was first evidenced by the decreased peak plasma total cortisol concentration observed in patients after injection of a 100 mg hydrocortisone bolus[7]. Such an increased cortisol distribution volume expectedly lowers the incremental rise in total plasma cortisol in response to ACTH; however, the amount of cortisol released from the adrenal cortex in response to ACTH may well be normal or even high but is diluted out in a larger distribution volume[7,11,12]. A 2018 study showed that most, if not all, critically ill patients present with low incremental total cortisol responses in response to ACTH tests, which is a result of the increased cortisol distribution volume and the low levels of cortisol-binding proteins, while free cortisol responses to ACTH are normal or sometimes even higher than normal[11]. Thus, an ACTH stimulation test cannot provide reliable information on the adrenocortical integrity or functional reserve.

Patients at risk of adrenocortical dysfunction. The most severely ill patients, particularly those with septic shock[46], have the most pronounced suppression of high-affinity CBG levels and, therefore, it is unsurprising that the incremental total cortisol responses to 250 µg ACTH in these patients are often <9 µg/dl, without indicating adrenocortical dysfunction[11,105]. Such low cortisol responses to ACTH injection are predictive of poor outcome[105], which is expected, given that high-affinity CBG levels are more suppressed in the sickest patients who have the highest risk of death than the levels in less sick patients[46]. The continuing controversy after large RCTs failed to confirm a mortality benefit conferred by stress doses of hydrocortisone in patients with septic shock suggests that septic shock is not the factor that predisposes to adrenocortical dysfunction in the ICU.

Alternatively, if central adrenocortical suppression is exerted by feedback inhibition through either plasma free cortisol levels that are elevated via peripheral drivers or other ligands that can bind to the hypothalamic glucocorticoid receptor[12], it may be possible that a long duration of critical illness predisposes to central hypoadrenalism[12,123] (FIG. 1). Indeed, a 2018 study showed that a longer duration of intensive care dependency suppressed the ACTH response to CRH injection; this effect was seen whether or not patients had sepsis or septic shock[12]. The structure and function of the adrenal cortex depend on the presence of appropriate levels of ACTH signalling[124]. A study of adrenal glands obtained post-mortem from patients with extended stays in ICU, who had been critically ill for several weeks, demonstrated structural and functional abnormalities; adrenal glands showed lipid droplet depletion, loss of zonational

Cortisol distribution volume
The theoretical volume in which a known amount of cortisol is dissolved to bring about a specific plasma concentration. In healthy individuals, >90% of plasma cortisol is protein-bound, which limits the distribution volume of cortisol.

Box 2 | **Contradicting guidelines and our proposed novel conceptual framework**

- Surviving sepsis campaign[131] (2016) guidelines advise against using intravenous hydrocortisone to treat patients with septic shock if adequate fluid resuscitation and vasopressor therapy are able to restore haemodynamic stability. If this is not achievable, 200 mg of intravenous hydrocortisone per day is suggested (weak recommendation and low quality of evidence).
- Critical-illness-related corticosteroid insufficiency guidelines[14] (2017) suggest using up to 400 mg of hydrocortisone per day in patients with septic shock that is not responsive to fluids and who require moderate-dose to high-dose vasopressor therapy (conditional recommendation, low quality of evidence).
- Our proposed novel conceptual framework suggests that the proposed doses of intravenous hydrocortisone (200–400 mg per day) do not take the suppressed cortisol metabolism during critical illness into account and may therefore be too high. In addition, the administration of such high doses of hydrocortisone to patients with septic shock does not bring about the expected mortality benefit and may have long-term adverse events.

structure and decreased ACTH-regulated gene expression[125]. As such, adrenal function in patients who stay in the ICU for extended periods of time may be negatively affected by decreased ACTH secretion. This hypothesis may explain why patients who are critically ill and have been in the ICU longer than 4 weeks have suppressed plasma levels of total cortisol and free cortisol, which are no longer higher than levels in healthy individuals[11]. By contrast, patients who survived had increased (supranormal) plasma ACTH, total cortisol and free cortisol levels 1 week after being discharged from the ICU[11]. Whether the reversibility of the alterations to the HPA axis contributed to patient survival remains unclear. Although an exact threshold level for diagnosing insufficient systemic cortisol availability remains unknown, this hypothesis can be further investigated via RCTs that investigate the outcome effect of either a lower dose of hydrocortisone among all long-stay ICU patients, which would take the persistently suppressed cortisol breakdown into account, or prevention and/or treatment with ACTH or CRH.

Safety of current recommendations

Given that the half-life of cortisol is 5–8-fold longer during critical illness than during health, doses of 200–400 mg of hydrocortisone per day, which are advised by 2017 practice guidelines[14], are probably too high. However, the large RCTs (TABLE 1) on the effect of such doses of hydrocortisone in septic shock showed no uniform mortality benefit but also no serious short-term harm, apart from more pronounced hyperglycaemia in all studies[113–116]. By contrast, most studies showed the reversal of shock and earlier weaning from mechanical ventilation[113–116] (TABLE 1). Clinicians may therefore conclude that it is safe to treat patients with septic shock with 200–400 mg of hydrocortisone per day[126]. However, a recent large follow-up study of 1,440 children, who had been treated in the paediatric ICU, identified use of glucocorticoids while in the ICU as an independent risk factor for poor neurocognitive development 2 years later[127]. Thus, the long-term safety of stress doses of hydrocortisone remains unproven.

Conclusions

Accumulating evidence suggests that the amount of cortisol that is produced in human patients with critical illnesses is not much higher, if at all, than that produced in healthy patients. Instead, the increased availability of systemic cortisol during critical illness seems to be largely driven by decreased levels of cortisol-binding proteins in the circulation and by decreased cortisol breakdown in the liver and kidney. Circulating free cortisol that is elevated via such peripheral mechanisms may partially explain why ACTH levels are low rather than high in ICU patients. This mechanism may be mediated by free cortisol-induced feedback inhibition and/or by elevated circulating levels of bile acids, both of which can bind to the hypothalamic glucocorticoid receptor, thereby suppressing CRH expression, AVP action and ACTH release. When low ACTH levels are present for an extended period of time, this may negatively affect adrenocortical integrity and function.

Assessing adrenal integrity and function in critically ill patients with the use of a 250 µg ACTH stimulation test has shown to be invalid, as the test results are confounded by the increased cortisol distribution volume found in these patients. Current guidelines advise the treatment of patients with septic shock with 200 mg of hydrocortisone daily, which increases blood pressure and reduces inflammation but without any proven mortality benefit[115,116]. These doses of hydrocortisone do not take the substantially increased half-life of cortisol into account, are thus probably too high and may further increase central adrenocortical suppression via feedback inhibition. In addition, the long-term safety of stress doses of hydrocortisone with regard to long-term physical and neurocognitive functioning is currently not proven and may be problematic. Future research should focus on critically ill patients who have the potential to have an extended ICU stay, who might be at risk of developing central hypoadrenalism. Furthermore, research on novel strategies to prevent and/or treat this complication, such as lower doses of hydrocortisone or infusion of ACTH or CRH, is needed. Long-term physical and neurocognitive outcomes should be pre-planned outcomes of future RCTs.

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