Limitations in the Design of Critical Care Studies and Suggestions for Future Research Directions

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ABSTRACT

Glucocorticoid (GC) therapy has been a cornerstone of critical care; however, its full potential has been constrained by fixed-dose regimens and trial designs that predate current insights into the dynamic, phase-specific functions of glucocorticoid receptor α (GRα). This study shifts focus from mechanistic pathways to the clinical implications of phase-adaptive care, emphasizing how GC therapy can be optimized through individualized, response-guided strategies tailored to illness trajectory and biological variability. Rather than reiterating GRα's mechanistic role, which is discussed in Chapter 3, this work highlights its practical relevance in therapeutic decision-making across the three sequential phases of critical illness: priming, modulatory, and restorative. In this clinically oriented framework, phase-specific treatment adjustments are informed by real-time changes in systemic stress markers, immune dynamics, and metabolic indicators. Earlier randomized controlled trials were instrumental in establishing safety but often failed to account for evolving physiological demands or receptor variability, contributing to inconsistent outcomes. To bridge this translational gap, this study proposes the integration of response-guided protocols utilizing accessible clinical biomarkers—such as C-reactive protein, interleukin-6, D-dimer, and lactate—allowing for adaptive dosing and tapering strategies aligned with patient-specific recovery patterns. Moving beyond pharmacologic dosing, the study outlines adjunctive clinical strategies—including targeted micronutrient supplementation and microbiome-supportive therapies—not as theoretical possibilities but as practical co-interventions that can be incorporated into intensive care unit protocols. Furthermore, it explores how artificial intelligence-enabled clinical decision systems and adaptive trial designs can operationalize precision care by dynamically stratifying patients and tailoring interventions to shifting biological profiles. Together, these applied strategies support a transition from static treatment paradigms to a precision medicine model in critical care—one that aligns GC therapy with individualized recovery trajectories, maximizes therapeutic responsiveness, and reduces treatment-related risks through multimodal, phase-responsive interventions.

Keywords Critical Illness, glucocorticoid treatment, phase-specific therapy, homeostatic correction, biomarker-guided treatment, micronutrient and microbiome integration

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Introduction

Glucocorticoid (GC) therapy has been a cornerstone of critical care due to its well-established anti-inflammatory and immunomodulatory effects. These benefits are mediated by glucocorticoid receptor α (GRα), a ligand-activated transcription factor that coordinates immune, metabolic, vascular, and neuroendocrine functions. However, its therapeutic impact has been limited by traditional fixed-dose regimens and trial designs that do not account for biological variability or changing illness dynamics.

Recent systems biology research reveals that GRα activity follows a phase-dependent pattern, corresponding to the sequential progression of critical illness. This evolving understanding supports a three-phase treatment model—priming, modulatory, and restorative—each marked by distinct therapeutic priorities and biological responses.

Building on this knowledge, this study proposes a clinically actionable, response-guided approach to GC therapy that adjusts interventions based on patient-specific illness trajectories. It emphasizes practical clinical tools, including phase-specific biomarkers (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], D-dimer, lactate) to inform real-time treatment decisions.

It also explores adjunct micronutrient and probiotic strategies to support GRα function, along with artificial intelligence (AI)-assisted trial design and patient stratification as tools for precision care. Together, these innovations form a biologically informed, multimodal framework aligned with the complexity of critical illness.

GC–GRα Signaling as a Central Regulator of Adaptive Homeostasis

GC therapy remains one of the most effective interventions for regulating systemic homeostasis and promoting recovery in critically ill patients. While the mechanistic underpinnings of GC-GRα signaling have been thoroughly reviewed in Chapter 3[1] ("Factors Influencing Glucocorticoid Treatment Response: Mechanism-Based Strategies to Overcome Glucocorticoid Resistance and Restore GRα Function"), this section focuses on the clinical implications of GRα as a therapeutic target, emphasizing its role in guiding personalized treatment based on disease dynamics. The diverse effects of GC-GRα signaling influence not only inflammation but also metabolism, hemodynamic stability, mitochondrial function, neuroendocrine responses, and tissue repair, all of which are critical to patient outcomes in intensive care.

GC–GRα Signaling and Phase-Specific Homeostasis

Building on recent insights, GRα activity is increasingly recognized as a clinical marker of phase-specific homeostatic demands in critical illness, distinguishable across priming, modulatory, and restorative phases.[2] This section highlights how GRα signaling informs treatment timing, intensity, and monitoring. Clinically, this approach supports more responsive management of endothelial integrity, immune modulation, mitochondrial function preservation, and hemodynamic support, all central to achieving recovery milestones in intensive care unit (ICU) patients.[3]

Limitations of Conventional Glucocorticoid Protocols

This evolving systems-level understanding challenges the long-standing reliance on standardized GC regimens, which are based on static, empirical drug models that lack mechanistic grounding, including the author's previous work. For over 50 years, most RCTs have employed a fixed-dose, fixed-duration (7–10 days) protocol, without considering individual illness trajectories, biological variability, or the phase-specific needs of critical illness. These traditional approaches stand in contrast to the growing rationale for dynamic, response-guided treatment informed by physiological markers and real-time biomolecular feedback.

Historical Perspective: from Flexible Use to Protocolization

Historically, GCs were administered in a flexible manner in early critical care practice. In conditions like ARDS and Pneumocystis carinii pneumonia, early randomized trials incorporated dose titration based on clinical response, a strategy that was widely accepted and effective.[4] However, in the late 20th century, industry-supported, protocol-based models promoted rigid, one-size-fits-all dosing. These protocols abandoned response-based strategies, omitted tapering guidelines, and failed to report complications related to abrupt discontinuation. As a result, withdrawal-related issues were often misattributed to GC toxicity, leading to persistent misattribution bias.[5] Meanwhile, with the rise of biologics, the GC narrative shifted toward emphasizing risks, overshadowing their mechanistic rationale and clinical value.

Systems Biology of GRα: Interdependence with Mitochondria, Micronutrients, and Microbiota

Importantly, GC-GRα signaling does not function in isolation; its effectiveness depends on coordinated interaction with mitochondrial function, redox balance, micronutrient levels (such as vitamins A, C, D, E, B complex, zinc, selenium, magnesium, and iron), and microbial integrity, all of which fluctuate dynamically throughout illness.[3] For detailed mechanisms, see Chapter 3 ("Factors Influencing Glucocorticoid Treatment Response: Mechanism-Based Strategies to Overcome Glucocorticoid Resistance and Restore GRα Function").[1] Here, the focus is on clinical strategies to address these interdependencies through supportive co-interventions and treatment adjustments. Despite these complexities, most RCTs to date remain anchored in an outdated framework that views GCs primarily as broad-spectrum anti-inflammatory agents. This limited perspective neglects their role as systemic hormone-receptor-based regulators of adaptive homeostasis, orchestrating the transcription of gene networks essential for biological adaptation across the phases of critical illness. Specifically, GC–GRα signaling activates immune and survival pathways during the early (priming) phase, promotes the resolution of inflammation in the middle (modulatory) phase, and supports tissue repair and physiological recovery in the late (restorative) phase.

Call for a New Phase-Based, Response-Guided Framework

To address these fundamental limitations, a new framework is urgently needed—one that views GC therapy not as a static pharmacological input, but as a dynamic, phase-specific intervention. This model would incorporate clearly defined phase-specific interventions, continuous biomarker monitoring (e.g., IL-6, CRP, D-dimer, lactate), and real-time adjustments, including supportive co-therapies, beyond dose and duration, based on evolving physiological and immunological signals. Such an approach has the potential to reduce therapeutic failures linked to nonresponsiveness and enhance clinical outcomes by aligning treatment with the patient's biological trajectory. Before adopting this approach, it is essential to identify the key methodological flaws in legacy RCTs that have constrained the full clinical potential of GC therapy in critical illness.

Systemic Functions of GC–GRα Signaling and Phase-Specific Therapeutic Effects

Multi-Systemic Regulation Beyond Anti-Inflammation

GCs, through GRα activation, regulate key physiological systems affected in critical illness, including inflammatory, metabolic, mitochondrial, vascular, immune, endocrine, coagulation, neurological, and epithelial systems. Their actions extend beyond anti-inflammatory effects, establishing GRα as a central coordinator of systemic recovery.[6] GCs contribute to the maintenance of endothelial barrier integrity, regulate vascular tone, and enhance mitochondrial bioenergetics by boosting redox pathways, preserving ATP stores, and reducing oxidative damage. They also influence immune cell trafficking and differentiation, support electrolyte and fluid balance, and modulate neuroendocrine signaling. Collectively, these functions protect high-demand

organs from energy failure, oxidative stress, immune dysregulation, and organ dysfunction during acute systemic stress.[7]

Immune Modulation without Immunoparalysis

At the immune level, GC–GRα signaling orchestrates key immune regulatory functions by modulating leukocyte trafficking, promoting lineage-specific differentiation, and inducing apoptosis of activated immune cells—thereby mitigating hyperinflammation without inducing immunoparalysis. It reprograms antigen-presenting cells and preserves innate–adaptive immune crosstalk, enabling immune recalibration that ensures effective pathogen clearance while minimizing tissue damage. These immunomodulatory effects are phase-dependent: during the priming phase, GCs enhance innate defenses, whereas in the modulatory and restorative phases, they facilitate anti-inflammatory resolution and immune realignment.[6]

Neuroendocrine Reset and Metabolic Rebalancing

GCs reset the hypothalamic–pituitary–adrenal (HPA) axis and restore autonomic tone, both disrupted by prolonged systemic stress. They also support the reestablishment of metabolic homeostasis by lowering catabolic hormones and enhancing insulin sensitivity.

Vascular, Coagulation, and Fibroproliferative Control

GCs regulate coagulation and fibroproliferation by suppressing pro-thrombotic signaling, reducing fibrin deposition, and promoting vascular stability. They also attenuate fibroproliferative remodeling and prevent excessive extracellular matrix buildup in conditions such as ARDS.[7,8]

Preservation of Epithelial Barriers and Circadian Rhythms

GCs also preserve gastrointestinal and epithelial barrier integrity, minimizing pathogen translocation and endotoxin exposure. They strengthen barriers by stabilizing tight junctions and supporting epithelial turnover. GCs additionally restore circadian rhythms, which are often disrupted in the ICU by constant light and sedatives, thereby promoting systemic homeostasis and synchronized physiological recovery.

Alignment with the Phases of Critical Illness

GC effects are highly phase-specific: they enhance adaptive responses in the priming phase, suppress inflammation during the modulatory phase, and promote tissue repair in the restorative phase. These actions reflect the evolving pathobiology of critical illness, supporting host defense, organ protection, and recovery. When appropriately timed, GC–GRα signaling stabilizes systemic physiology, reduces organ dysfunction, accelerates recovery, and may lower required GC doses while improving outcomes.

Micronutrient and Microbiome-Based Strategies to Enhance GRα Function

Rationale for Adjunctive GRα-Supportive Strategies

This section builds on Chapter 2,[7] highlighting the adjunctive role of micronutrients and microbiota-targeted therapies in enhancing GRα responsiveness during critical illness. An integrative strategy is essential for optimizing GRα function and minimizing overall GC burden. Adjunctive interventions—including targeted supplementation with essential micronutrients (such as vitamins A, C [a potent antioxidant], D, E, B complex, zinc, selenium, and magnesium), circadian regulators (like melatonin), and microbiome-supportive probiotics—enhance GRα transcriptional activity and support the body's intrinsic homeostatic regulation. These co-interventions help sustain mitochondrial function, preserve barrier integrity, and reduce inflammation.[3,7] Such supportive strategies may help reduce required GC dosages and shorten treatment duration while improving patient-centered outcomes.

Mitochondrial-Targeted Antioxidants and Melatonin

Although mitochondrial dysfunction and oxidative stress are key factors in critical illness, mitochondrial-targeted antioxidant therapies in the ICU remain largely experimental. Among available options, vitamins C and E—particularly when used in combination—consistently reduce oxidative damage and prevent organ dysfunction.[9,10] Selenium and zinc further enhance antioxidant defenses and mitochondrial function through glutathione peroxidase and metallothionein pathways, both of which are linked to GRα regulation, especially in sepsis and ARDS.[11,12] Melatonin, with both antioxidant and circadian-regulating properties, shows promise in neurocritical care and sepsis models; however, its use in the ICU is still under investigation.[13] For a full review, see Chapter 3.[1]

Synergistic Integration of GCs, Probiotics, and Micronutrients

Emerging evidence supports the combined use of GCs, probiotics, and targeted micronutrients to address the multifactorial pathobiology of critical illness.[3] This integrated approach combines response-guided GC therapy with GR-supportive co-interventions to enhance therapeutic efficacy, reduce adverse events, and align treatment with adaptive physiological processes. Restoring GC responsiveness in cases of acquired resistance may be achievable through these combined therapies, offering an accessible and scalable adjunctive strategy.

Probiotics as Immunobiotic Modulators

As reviewed in Chapter 2 ("The Glucocorticoid System: A Multifaceted Regulator of Mitochondrial Function, Endothelial Homeostasis, and Intestinal Barrier Integrity"),[7] probiotics are essential not only for correcting dysbiosis but also for restoring systemic homeostasis. They reinforce intestinal barrier integrity, attenuate systemic inflammation, and modulate the gut–immune–brain axis, collectively contributing to multisystem recovery.[3] Mechanistically, probiotics stabilize tight junctions, inhibit NF-κB signaling, and promote the expansion of T regulatory cells. Certain strains enhance GR signaling by reducing oxidative stress, increasing GRα sensitivity, boosting nuclear signaling, and stabilizing the HPA axis. This interaction protects mucosal surfaces and amplifies the systemic effects of GC therapy. When combined with GC and micronutrients, probiotics help restore immune balance, maintain barrier integrity, and support multiorgan recovery.[3,7]

Functional Roles of Targeted Micronutrients

Alongside probiotics, targeted micronutrients play a crucial role in regulating GRα and supporting systemic recovery. These micronutrients can be categorized based on their primary functions in GRα signaling and homeostatic regulation. Essential vitamins—specifically D, A, C, and E—act synergistically with GRα to enhance immune function, strengthen cellular defense, and promote tissue repair. Vitamin D, through its receptor (VDR), regulates the expression of over 1,000 to 3,000 genes, depending on the tissue type, many of which overlap with GRα pathways involved in immune resolution and epithelial repair. It also stimulates the synthesis of antimicrobial peptides, further enhancing the immune defense mechanisms.[14–16] Vitamin A plays a critical role in maintaining epithelial integrity and supporting mucosal immunity during systemic stress.[17,18] Vitamin C contributes to the neutralization of reactive oxygen species, regeneration of other antioxidants, and maintenance of cellular redox balance.[3,19] Vitamin E functions as a lipid-soluble antioxidant, stabilizing cellular membranes and modulating redox-sensitive signaling pathways to protect tissues from oxidative damage.[20]

B-Vitamins, Zinc, Selenium, and Magnesium in GRα Regulation

The B-complex vitamins support mitochondrial function, neurotransmitter production, and immune system regulation,[21,22] functions that are critical for maintaining cellular resilience under stress. Zinc and selenium stabilize the GRα binding domain and support redox-sensitive chaperone proteins like HSP90. In addition, they enhance antioxidant defenses by regulating superoxide dismutase.[23] Together, these micronutrients optimize GRα activity and improve cellular redox capacity under stress. Magnesium acts as a cofactor in ATP-dependent signaling pathways, supporting neuromuscular function, metabolism, and vascular tone.[24] Collectively, these micronutrients help maintain GRα function and promote physiological balance during periods of inflammation, oxidative stress, and multi-organ dysfunction.

Clinical Supplementation Strategies and Considerations

Micronutrient serum levels should be interpreted in the context of systemic inflammation, as acute-phase responses can mimic true deficiency.[25] Even mild CRP elevations lower levels of selenium and vitamins B6 and C. As the inflammation burden increases, levels of selenium and vitamins A, B6, C, and D may decrease by over 40%. Despite this, the increased metabolic demands of critical illness justify proactive supplementation, especially with thiamine, vitamins C and D, selenium, zinc, and iron. Severe vitamin D deficiency (<12 ng/mL) is consistently linked to worse outcomes.

In clinical practice, supplementation strategies should be adapted to the illness phase. During the early inflammatory surge (priming phase), early correction of common deficiencies is recommended. In the modulatory and restorative phases, supplementation may shift toward maintenance and targeted correction, including treatment of iron deficiency anemia guided by biomarkers such as hepcidin. High-dose intravenous iron therapy can be considered once inflammation subsides to minimize the risk of iron overload. Bolus doses of vitamin D are discouraged due to the risk of feedback inhibition and suboptimal activation; physiologic, combination supplementation is preferred, particularly in patients with prolonged ICU stays.[26] This strategy aims to sustain GRα signaling, reduce treatment complications, and support immune, endocrine, and barrier functions during recovery.

Mechanistic Links between Micronutrients and GRα Signaling

In-depth molecular mechanisms linking micronutrients to GRα regulation—including ligand binding, chaperone complexes (such as HSP90), nuclear translocation, and transcriptional activity—are fully addressed in Chapter 1 (section: "Comprehensive View of Glucocorticoid Biology"),[6] This process is highly sensitive to oxidative stress, redox imbalances, and mitochondrial dysfunction, all of which are common in critical illness. GRα-mediated transcription is highly dependent on optimal cellular redox balance, mitochondrial energy production, and availability of key cofactors involved in posttranslational modifications.

Micronutrient sufficiency—particularly involving antioxidants such as vitamins C and E, trace elements like selenium and zinc, and cofactors like magnesium—plays a supportive role in maintaining GRα receptor stability and transcriptional activity. By preserving mitochondrial function, reducing oxidative injury, and enhancing redox homeostasis, these micronutrients help sustain GRα responsiveness during illness.

Alignment with Temporal PHASEs of Homeostatic Correction

Micronutrients contribute differentially across the phases of critical illness, aligning with the evolving biological demands of the priming, modulatory, and restorative phases (**Table 1**).[3] and intracellular regulation of GRα signaling (**Fig. 1**).[19,27–35]

Supplementary Appendix 1 (available in the online version only) provides an expanded overview of how key micronutrients, including vitamins D, A, C, E, B-complex, and trace elements like zinc and selenium, support GRα function by stabilizing receptor structure, facilitating nuclear translocation, enhancing co-activator complex formation, and improving transcriptional efficiency. **Table 2** further details the phase-specific contributions of critical nutrients such as thiamine, vitamin D, and vitamin C across the priming, modulatory, and restorative phases of homeostatic correction. [31,36–85] Consistent with the recommendations of the European Society for Clinical Nutrition and Metabolism, proactive correction of micronutrient deficiencies during critical illness is encouraged. This includes early administration of these nutrients in sufficient quantities to support mitochondrial bioenergetics, reduce oxidative stress, and modulate inflammatory responses in alignment with the patient's biological phase.[86,87]

These vitamins and trace elements play distinct roles across the phases: supporting immune recalibration and oxidative balance during the priming phase, controlling inflammation and stabilizing endothelial function during the modulatory phase, and promoting tissue repair and hematopoietic recovery during the restorative phase. By aligning micronutrient therapy with the temporal

Table 1 Comprehensive homeostatic corrections functions

Phase	Key processes	Functions
Priming phase	HPA axis activation and early GRα-Inducible transcriptional response	a. HPA axis activation: initial ACTH-driven cortisol surge ensures metabolic and immune readiness. b. GILZ: inhibits NF-κB and AP-1 activity, promotes macrophage activation and neutrophil clearance, facilitating early immune homeostasis. c. DUSP1: deactivates MAPKs (ERK, JNK, p38), reducing cytokine production and limiting systemic inflammation; essential for GC anti-inflammatory action in multiple models
Priming phase	Activating innate immunity, bioenergetic supply, and cardiovascular response	a. Immune cell mobilization: activation and migration of T cells, B cells, NK cells, monocytes, neutrophils, and dendritic cells. b. Metabolic adaptation: mitochondrial biogenesis, increased glucose uptake, glycolysis, and fatty acid oxidation for energy supply. c. Innate immune enhancement: induction of acute-phase proteins (CRP, SAA) and upregulation of pathogen recognition receptors (TLR2, TLR4, NLRP3, P2Y2R). d. Transcription factor cooperation: GC-GRα works with NF-κB, AP-1, and TNF-α to increase chromatin accessibility and regulate immune response genes. e. Phagocytosis and pathogen killing: GILZ-driven upregulation of IFN-γ enhances macrophage activation and bacterial clearance. f. Cardiovascular adaptations: increased adrenergic receptor sensitivity, catecholamine synthesis, and NO-mediated vasodilation. g. Fluid balance regulation: GC-GRα interacts with mineralocorticoid receptors to modulate sodium retention and plasma volume. h. Antioxidant defense activation: upregulation of superoxide dismutase (SOD), GPx, and catalase to reduce oxidative stress and prevent tissue damage
Modulatory phase	Repressing inflammation, mitigating oxidative stress, and restoring vascular integrity	a. Suppression of inflammation: downregulation of NF-κB, AP-1, and MAPK signaling to control immune activation. b. Chromatin remodeling: GC-GRα increases accessibility to anti-inflammatory genes (MKP-1, IκBα, SGK-1). c. Endothelial Protection: Upregulation of SphK1 and Angpt-1 stabilizes endothelial junctions and prevents vascular permeability. d. Vascular function maintenance: GC-GRα enhances eNOS activity to sustain NO production and reduce vascular resistance. e. Prevention of secondary infections: GC-GRα preserves mucosal immunity and limits neutrophil dysfunction, lowering nosocomial infection risks. f. Oxidative stress mitigation: increased expression of glutathione peroxidase and SOD to neutralize ROS. g. Systemic homeostasis: GC-GRα balances immune activation with metabolic stability, ensuring energy resources are preserved. h. Neuroendocrine modulation: GC-GRα interacts with the HPA and autonomic nervous systems to fine-tune systemic responses to stress. i. Endothelial protection: GC treatment preserves endothelial glycocalyx, reduces edema, and sustains organ perfusion
Restorative phase	Resolving inflammation, facilitating tissue repair, restoring normal structure, and activating adaptive immunity	a. Inflammation resolution: pro-resolving mediators (AnxA1, ALXR, GILZ) dampen inflammation and restore immune balance. b. Apoptotic cell clearance: macrophages (M2/Mres) engulf apoptotic neutrophils, reducing inflammatory load. c. Macrophage polarization shift: transition from M1 (pro-inflammatory) to M2/Mres (pro-resolving) phenotypes to drive tissue repair. d. Tissue regeneration: upregulation of VEGF, FGF, and TGF-β supports angiogenesis, fibroblast activation, and ECM remodeling. e. Fibrosis regulation: GC-GRα fine-tunes SERPINE1 and MMP activity to prevent excessive fibrosis. f. Adaptive immune reactivation: restoration of T cell function, allowing for long-term immune memory formation and pathogen surveillance. g. Neutrophil clearance: GILZ expression promotes neutrophil apoptosis, preventing excessive inflammation. h. Cellular homeostasis: restoration of pH balance, oxygenation, and mitochondrial function to sustain energy production. i. Muscle preservation and recovery: GC-GRα regulates protein metabolism to prevent muscle atrophy and support regeneration. Organ functional recovery: restoration of normal tissue architecture and systemic equilibrium to achieve full recovery

Abbreviations: ACTH, adrenocorticotropic hormone; AP-1, activator protein-1; CRH, corticotropin-releasing hormone; DUSP1, dual specificity phosphatase 1; ERK, extracellular signal-regulated kinase; 5; GC, glucocorticoid; GILZ, glucocorticoid-induced leucine zipper; GR, glucocorticoid receptor; GRα, glucocorticoid receptor alpha isoform; HPA axis, hypothalamic-pituitary-adrenal axis; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

Note: This table outlines the key regulatory processes and functional outcomes orchestrated by glucocorticoid receptor alpha (GRα) across the three sequential phases of homeostatic correction in critical illness: priming, modulatory, and restorative. Each phase represents a coordinated set of GRα-mediated responses tailored to the host's evolving physiological demands. The priming phase initiates immune activation, metabolic adaptation, and vascular responsiveness. The modulatory phase focuses on suppressing inflammation, restoring redox balance, and preserving endothelial integrity. The restorative phase supports immune resolution, tissue repair, and reactivation of adaptive immunity. This integrated progression enables dynamic and proportionate responses to severe physiological stress, promoting the recovery of systemic homeostasis.[2]

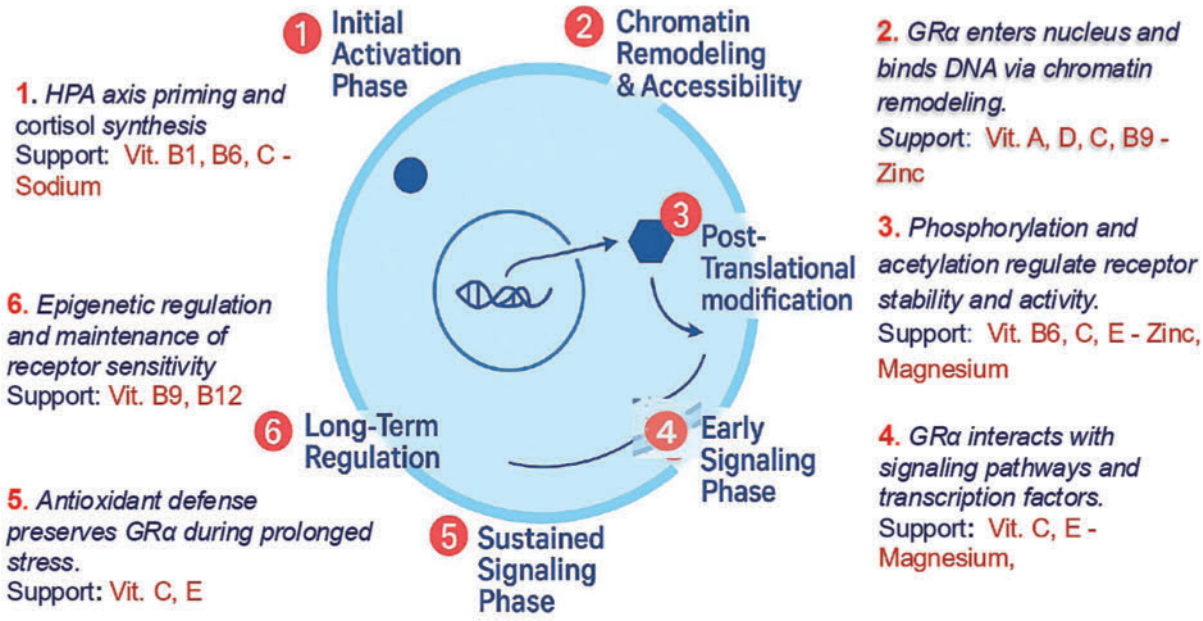

Fig. 1 Cellular phases of GRα activation and micronutrient regulation. This figure illustrates the sequential intracellular regulatory phases of glucocorticoid receptor α (GRα) activation, along with the specific micronutrients that modulate each phase. The activation and function of GRα proceed through six tightly regulated intracellular phases, each of which is supported by specific vitamins and trace elements. These micronutrients serve as essential cofactors for receptor activation, nuclear translocation, chromatin remodeling, and transcriptional regulation. They also help counteract oxidative stress and other pathophysiological disturbances that impair GRα signaling. This integrative micronutrient strategy enhances GC responsiveness and supports adaptive homeostatic corrections during critical illness. A comprehensive review and bibliography are provided in **Appendix 1** (available in the online version only).

Table 2 Role of thiamin, vitamin D, and vitamin C in the three phases of homeostatic correction

homeostatic Phase	Thiamin	Vitamin D	Vitamin C
Reinforce innate immunity	Supports innate immune function by enhancing neutrophil and lymphocyte activity. Stimulates neutrophil migration and lymphocyte proliferation, protects immune cells from oxidative stress, and reduces dendritic cell cytokine production by shifting metabolism from glycolysis to oxidative phosphorylation[36,37]	Supports the innate and adaptive immune system. ⇑ TLR coreceptor CD14. ⇑ antimicrobial peptides cathelicidin and LL-37.[38] ⇑ neutrophil recruitment, activation, and function.[39] ⇑ antibacterial activity[40]	Supports neutrophil anti-bacterial function at hypoxic inflammatory sites.[41] ⇑ neutrophil and macrophage chemotaxis, phagocytic capacity, lysozyme activity for cell elimination, and bacterial killing.[41–43] Supports lymphocyte proliferation and differentiation.[41] ⇑ production of type I interferons (IFNs) for anti-viral immune responses against influenza virus infection[44]
Bioenergetic supply	Essential for energy metabolism and carbohydrate breakdown/ATP production.[45] Thiamin pyrophosphate is a cofactor for PDH, a-KGDC[46]	⇑ mitochondrial number, morphology, physiology, and expression of key mitochondrial proteins, resulting in increased ATP synthesis[47]	⇑ ATP synthesis[48]
Vascular integrity		Modulate endothelial function (nongenomic up-regulation of eNOS gene expression) and vascular permeability (prevents the formation of intracellular endothelial gaps) via multiple genomic and extragenomic pathways.[49] Protective effect on the alveolar capillary membrane[50]	Improves endothelial permeability, microvascular and macrovascular function.[51] Preserves endothelial barrier integrity[52] in synergy with GC.[53] Cofactor for dopamine and vasopressin.[54] Downregulator of NET formation in sepsis[43,55]
Repress inflammation	Exerts significant anti-inflammatory effects: (i) ⇓ activation of p38-MAPK, (ii) ⇓ degradation of Ik-Ba, and (iii) ⇑ activation and nuclear translocation of NF-kB, ⇓	⇑ GR concentration[59] and GC function.[31] ⇓ synthesis of TNF-a and IL-1b.[40] ⇑ GC-mediated MKP-1 ⇒ ⇓ p38 MAPK-mediated inflammatory genes.[31,60,61]	Cofactor for GC synthesis.[66] Improves GR function.[67] Reverses oxidation of the GR.[68] GC facilitates Vit C cellular uptake.

Table 2 (*Continued*)

homeostatic Phase	Thiamin	Vitamin D	Vitamin C
	expression of cytokines and chemokines, iNOS, and COX-2.[56] ⇓ nuclear NF-kB/p65 protein level, ⇑ IL-10 synthesis—⇓ synthesis of iNOS, COX-2, Hsp70, TNF-a, and IL-6.[57] Sinergy with glucocorticoids in inhibiting IL-6 transcription[58]	⇑ IkBa expression ⇒ ⇓ NF-kB.[62,63] GR represses Vitamin D inactivator CYP24A1. Suppresses Th1 and Th17 cell activity while promoting regulatory T cell development, restoring immune balance, and reducing pro-inflammatory cytokine production[64,65]	⇓ synthesis of TNF-α and IL-6.[69] ⇓ Ik-Ba degradation ⇒ ⇓ NF-kB activation and nuclear translocation. ⇓ macrophage activation by modulating MAPK[70]
Repress oxidative stress	⇑ Transketolase, a key enzyme for the pentose phosphate pathway and for the synthesis of NADPH with glutathione cycling, an important antioxidant pathway[71]	VDR is a GR target for PGC-1a induction a.[72] Protective against ROS production.[73] ⇑ Glutathione and glutamate formation ⇒ ⇓ ROS formation[74]	General role: electron donation as one of the most potent antioxidants. Suppress NADPH oxidase (NOX) pathway.[67] Prevents the depletion of other circulatory antioxidants, such as lipid-soluble vitamin E and glutathione.[52] Scavenges ROS and peroxynitrite; protects mitochondrial membranes and respiratory chain enzymes, preserving redox balance and ATP synthesis during oxidative stress[48,75]
Resolve and restore anatomical function		Restore alveolar epithelial barrier, promoting the proliferation of type 2 epithelial cells, and inhibiting fibroproliferation[50,76]	⇑ expression of pro-resolution and wound healing biomarkers, improved matrix organization, angiogenesis, and collagen deposition consistent with adaptive repair.[77] ⇑ neutrophils apoptosis and clearance from inflammatory sites.[78] ⇑ Collagen synthesis, recycles other antioxidants, improves wound healing[54,77]

Abbreviations: ⇑, increase; ⇓, decrease.
Note: Summary of the coordinated roles of thiamin, vitamin D, and vitamin C in the three phases of homeostatic correction. The table highlights their shared and distinct functions in enhancing innate immunity, supporting mitochondrial energy production, preserving vascular integrity, repressing inflammation and oxidative stress, and promoting tissue repair and resolution.

phases of homeostatic correction, clinicians can fine-tune GRα receptor responses and enhance signaling efficiency.[1]

Evidence Gaps and Opportunities for Future Trials

While meta-analyses[88] and systematic reviews[10,89–91] suggest potential benefits of micronutrient and probiotic supplementation in critical illness, these findings are limited by clinical heterogeneity and the inclusion of biologically diverse patient populations. Reported outcomes often reflect average treatment effects, which may obscure meaningful benefits in biologically defined subgroups, particularly those with documented micronutrient deficiencies or biomarker-identified immune dysregulation.

A key limitation in existing research is the absence of biological stratification, limited use of response-guided treatment models, and infrequent sequential monitoring of micronutrient levels, all of which constrain the ability to assess treatment responsiveness over time. Most trial designs lack biological stratification, response-guided approaches, or sequential micronutrient measurements, making it challenging to evaluate treatment responsiveness over time.

The synergistic combination of hydrocortisone, vitamin C, and thiamine, originally proposed by Marik et al,[92] remains clinically compelling but lacks validation from large prospective trials, highlighting a significant evidence gap. Meanwhile, large RCTs indicate that early full nutritional support (within 4–7 days) may cause dose-dependent harm, regardless of whether it is provided via enteral or parenteral routes.[93]

Collectively, these findings highlight an opportunity for future research to explore stratified trial designs that consider biological heterogeneity, incorporate dynamic biomarker monitoring, and evaluate phase-specific supplementation strategies in conjunction with GC therapy.

Toward a Coherent Multi-Modal Strategy

Emerging data suggest that a multimodal approach targeting key drivers of critical illness—such as dysregulated systemic inflammation, endothelial and epithelial dysfunction, dysbiosis, and oxidative stress may offer clinical benefits (reviewed in Chapter 2).[7] In the priming phase, these combined interventions contribute to a biologically cohesive and potentially synergistic framework: GCs modulate inflammatory responses, direct immune cell trafficking, and stabilize vascular tone and endothelial integrity; probiotics help restore microbial diversity, reinforce gut barriers function, and reduce endotoxin translocation; and micronutrients—particularly D, A, C, E, and the B-complex—enhance redox balance, mitochondrial bioenergetics, and immune responsiveness. This

physiology-aligned low-risk strategy may reduce GC dosage requirements, restore vascular and gut barrier integrity, improve immune and hemostatic balance, and promote recovery. In addition to supporting GC–GRα signaling, micronutrient repletion may contribute to overall organ protection and stabilization of homeostatic processes during critical illness.

Redesigning Clinical Trials for Complex, Multisystem Disorders: Toward Precision and Integration

Evaluating multimodal, physiology-aligned strategies in critical illness requires a shift away from conventional trial designs toward precision frameworks that account for biological heterogeneity and the evolving pathophysiology of systemic conditions such as sepsis.

Traditional randomized controlled trials (RCTs), typically designed for discrete, uniform diseases, are often insufficient to capture the variable treatment responses observed in critical illness. In contrast, precision trial designs offer greater flexibility by accommodating complex illness trajectories and the high case-mix heterogeneity inherent in multisystem conditions like sepsis. This approach does not compromise methodological rigor; instead, it strengthens the scientific validity of clinical trials by embedding randomization within mechanism-based, endotype-driven frameworks. Such designs enable the assessment of therapeutic effects across biologically defined subgroups, improving the relevance and applicability of trial findings.

Emerging trial platforms such as PALETTE—the "Adaptive Platform Trial for Personalization of Sepsis Treatment in Children and Adults" (identifier: NCT06381661)-and its pilot PROVIDE exemplify this new paradigm. PALETTE employs adaptive, phenotype-guided, domain-based randomization to assess the interaction among multiple interventions, including GCs, immunomodulators, anticoagulants, and micronutrient-based supportive therapies, in biologically defined subgroups. These designs are well-suited to reveal therapeutic synergies and individual responses in critical illness, where traditional RCTs have often failed to deliver clinically actionable results.

To operationalize precision medicine in the ICU, adaptive trial designs offer a flexible, data-driven framework that addresses the biological heterogeneity of critical illness while preserving scientific rigor. These designs allow dynamic adjustment of trial parameters based on interim data, improving efficiency, ethical alignment, and clinical relevance. Successfully employed in major platform trials, adaptive methods are essential for evaluating multimodal interventions in biologically diverse ICU populations. These elements include, but are not limited to:

1. Response-adaptive randomization adjusts treatment allocation in real time based on accumulating outcomes, ensuring more patients receive promising therapies. REMAP-CAP (community-acquired pneumonia)[94] demonstrated its feasibility and ethical advantages by dynamically guiding ICU patients toward more effective immunomodulators.
2. Interim analyses are predefined evaluations of efficacy, futility, or safety that enable timely, evidence-based trial modifications. PROVIDE, the pilot for PALETTE, uses interim assessments to halt ineffective interventions early, preserving resources, protecting participants, and accelerating conclusions.
3. Sample size re-estimation accounts for evolving outcome variability or event rates. Used in REMAP-CAP[95] and I-SPY 2,[94] it ensures trials remain adequately powered without over-recruitment, even in dynamic clinical contexts.
4. Adaptive enrichment refines eligibility criteria during a trial to focus enrollment on subgroups more likely to benefit. Guided by baseline biomarkers or phenotypes, it is used in the PALETTE platform, which stratifies patients by immunologic endotypes such as hyperinflammation and immunoparalysis.
5. Multiple domain randomization with biomarker-guided stratification enables simultaneous testing of therapies—like corticosteroids, immunotherapies, and anticoagulants—within distinct biological strata, improving detection of meaningful effects. Both REMAP-CAP[94] and PALETTE demonstrate their scalability and clinical relevance.
6. Hierarchical outcome modeling integrates multiple endpoints —mortality, duration of organ support, and recovery milestones—into a unified framework. Used in the CITRIS-ALI[96] and adapted for PROVIDE, it offers a more holistic assessment of interventions across complex ICU trajectories.

Together, these adaptive elements form the methodological core for a next-generation research platform, aligning treatment with individual biology. They overcome long-standing limitations of conventional RCTs in critical care, paving the way for more precise, effective, and patient-centered therapeutic strategies.

Crucially, adaptive components are not meant for universal use. Their selection should depend on specific clinical questions, intervention type, and level of biological heterogeneity. When used strategically, these tools enhance trial sensitivity, particularly in complex, multisystem conditions such as sepsis and ARDS, where traditional designs often fail to capture variable therapeutic responses. By tailoring trial design to changing pathophysiology and patient-specific biomarkers, this adaptive approach enables the implementation of truly personalized, mechanism-based therapies in the ICU.

Biomarkers to Guide Glucocorticoid Therapy and Monitor Homeostatic Correction

Laboratory biomarkers and combined clinical scores are increasingly recognized as valuable tools for identifying patients who may benefit from GC therapy, as well as for detecting those at risk of suboptimal response or potential harm. To date, however, most predictive models have been developed within the context of fixed-dose treatment protocols, limiting their ability to capture biological feedback and account for the dynamic nature of critical illness. Greater therapeutic precision may be achievable through adaptive, biomarker-integrated treatment approaches that better reflect the evolving pathophysiology of critical illness. Such response-guided strategies could support real-time treatment adjustments, facilitate early identification of nonresponders, and guide the timely addition of supportive therapies, thereby enabling more personalized and phase-appropriate clinical decisions.

Biomarkers can be generally classified into two main categories. Predictive biomarkers help identify patients likely to respond to treatment prior to initiation, supporting early stratification and

individualized therapeutic strategies. In contrast, monitoring biomarkers assess ongoing therapeutic responses and track the progression of homeostatic recovery. Together, these tools facilitate dose adjustments, therapy modifications, and determining the optimal timing for additional interventions, such as micronutrient supplementation or microbiome-based therapies.

Biomarkers Predictive of Glucocorticoid Responsiveness in Pneumonia, Sepsis, and ARDS

Emerging evidence has identified several biomarkers associated with GC responsiveness across pneumonia, sepsis, and ARDS (**Table 3**). However, the majority of these studies have been conducted within the framework of static, fixed-dose treatment protocols, which may limit their applicability to adaptive or personalized approaches. **Supplementary Appendix 2** (available in the online version only) provides a detailed description of the individual biomarkers and a complete bibliography [5–7,97–144]; a summary is presented here.

In pneumonia, high CRP levels (particularly > 204 mg/L), elevated IL-6, D-dimer, and preserved lymphocyte counts are associated with improved corticosteroid responses, with validated thresholds established in both CAP and COVID-19 cohorts.

In sepsis, predictive insights remain more variable. While tools like the PERSEVERE-II score and immune gene signatures help identify subgroups with differential responses to steroids, markers such as IL-8 and sTNFR1 primarily serve a prognostic rather than a predictive role. Low or persistently decreased mHLA-DR (a major histocompatibility complex class II molecule involved in antigen presentation to helper T cells) is associated with worse outcomes and higher infection risk, yet its utility in predicting GC responsiveness remains unconfirmed.

In ARDS, biomarkers such as NT-PCP-III in fibroproliferative ARDS and elevated inflammatory markers (CRP, IL-6, ferritin, NLR, LDH) in COVID-19 ARDS offer early signals of treatment responsiveness. Notably, a high NLR consistently correlates with poor responsiveness to GCs.

In summary, these biomarkers hold significant promise for individualizing therapy, but broader validation within adaptive, personalized treatment models is essential to confirm their clinical utility.

Phase-Specific Biomarkers for Monitoring Homeostatic Correction

Effective GC therapy in critical illness requires alignment with both the sequential phases of homeostatic correction and the individual patient's biological responsiveness. Predictive biomarkers of GC responsiveness, particularly in conditions such as severe pneumonia, septic shock, and ARDS (summarized in **Table 3**), can facilitate early identification of patient subgroups most likely to benefit from GC therapy, supporting more informed decisions on timing, dosing, and treatment intensity. Integrating predictive biomarkers with phase-specific monitoring may further improve therapeutic precision by enabling treatment adjustments to the patient's evolving biological landscape.

Monitoring the three sequential phases of homeostatic correction—priming, modulatory, and restorative (**Table 1**)—is essential for personalizing GC therapy. Each phase is characterized by distinct biological priorities and pathophysiological processes that influence the optimal timing and effectiveness of treatment. Phase-specific biomarkers provide real-time insight into disease progression and treatment response, enabling clinicians to assess disease severity and adjust therapy duration and tapering strategies accordingly. Clinically, these biomarkers serve two main

Table 3 Predictive biomarkers of glucocorticoid responsiveness

Condition	Predictive insight (abbreviated)
Pneumonia	Cortisol-to-CRP ratio > 3 in TBI predicts hospital-acquired pneumonia risk and corticosteroid benefit[194]
	CRP ≥ 150 mg/L, IL-6 ≥ 20 pg/mL, D-dimer ≥ 2.0 µg/L predict survival with corticosteroids (COVID-19)[134]
	Lymphocyte count ≥ 1,000/mm^3 linked to better CRP reduction with corticosteroids (severe CAP)[195]
	Composite score (AST, LDH, ferritin, IFN-λ3) predicts corticosteroid need (COVID-19)[135]
	CRP > 204 mg/L linked to lower mortality with corticosteroids; validated in 2 RCTs[136]
Sepsis	PERSEVERE-II score stratifies risk; corticosteroids are harmful in high-risk pediatric septic shock[137]
	100-gene adaptive immunity signature identifies pediatric endotypes benefiting from corticosteroids[138]
	IL-8, sTNFR1 are prognostic but not predictive of GC response[196]
	Low/persistent mHLA-DR indicates immunomodulation need; predictive GC role unconfirmed[197,198]
ARDS	NT-PCP-III > 9 µg/L in BAL by day 7 predicts corticosteroid benefit in fibroproliferative ARDS[139]
	Elevated CRP, IL-6, ferritin, NLR, LDH (high COVID-19 ARDS mortality); high NLR (poor GC response)[140]

Abbreviations: ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BAL, bronchoalveolar lavage; CAP, community-acquired pneumonia; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; D-dimer, fibrin degradation product; GC, glucocorticoid; GRα, glucocorticoid receptor alpha; IFN-λ3, interferon lambda-3; IL-6, interleukin-6; IL-8, interleukin-8; LDH, lactate dehydrogenase; mHLA-DR, monocyte human leukocyte antigen–DR; NLR, neutrophil-to-lymphocyte ratio; NT-PCP-III, N-terminal procollagen type III; OR, odds ratio; PERSEVERE-II, pediatric sepsis biomarker risk model; PSI, pneumonia severity index; RCT, randomized controlled trial; sTNFR1, soluble tumor necrosis factor receptor 1; TBI, traumatic brain injury.
Note: Condition: Disease under investigation (e.g., pneumonia, sepsis, ARDS). Predictive insight (Abbreviated): Summary of biomarker or score associated with glucocorticoid responsiveness. Biomarker-based predictions vary with disease progression and treatment timing; adaptive validation is essential.

functions: (1) identifying the current phase of illness and (2) evaluating GRα activation and therapeutic responsiveness.

Table 4 summarizes these phase-specific biomarkers, highlighting their mechanistic relevance and clinical utility. When interpreted in the context, these markers facilitate response-guided treatment decisions, supporting a transition from fixed-duration regimens to personalized, biologically coherent therapy.

Priming Phase: Overview and Biomarker Applications

The priming phase reflects the early stage of critical illness characterized by inflammatory surges, endothelial dysfunction, and metabolic stress. Biomarkers such as CRP, IL-6, lactate, D-dimer, and mitochondrial DNA (mtDNA) typically peak during this phase, reflecting immune activation, endothelial injury, and metabolic stress. This phase involves the acute activation of the HPA axis, resulting in endogenous GC release to support homeostatic corrections. High baseline levels of these markers correlate with disease severity, while their trajectories after GC initiation offer dynamic feedback on treatment response.[145] A rapid decline in CRP and lactate within 48 to 72 hours indicates effective GRα signaling, improved homeostatic recovery, and favorable clinical outcomes.[98–100] Conversely, persistent elevation of these biomarkers may signal GC resistance, prompting reassessment of GC dosing, duration, or the adjunction of supportive therapies.[102,103]

Table 4 Key biomarkers for monitoring homeostatic imbalance and disease progression in critical illness

Biomarker	Definition	Pathophysiologic role	GC impact	Phase and clinical interpretation
C-reactive protein (CRP)	An acute-phase protein synthesized by the liver in response to IL-6	Reflects systemic inflammation and cytokine activation during acute illness	Rapid IL-6 mediated suppression; early decline predicts treatment success	Priming and modulatory; ≥50% decline within 48–72 h predicts lower mortality and guides dosing/tapering
Neutrophil-to-lymphocyte ratio (NLR)	A hematological index derived from neutrophil and lymphocyte counts	Indicates innate-adaptive immune imbalance; elevated in hyperinflammatory states	May normalize with GC therapy; persistent elevation suggests resistance or poor prognosis	Priming; helps stratify severity and response likelihood, especially in CAP and COVID-19
Interleukin-6 (IL-6)	A pro-inflammatory cytokine central to acute-phase responses	Drives CRP synthesis, leukocyte activation, and endothelial stress	Declines within 24–48 h post-GC in responsive patients	Priming and modulatory; high baseline IL-6 linked to poor outcomes; decline supports efficacy
Procalcitonin (PCT)	A peptide precursor of calcitonin, elevated in bacterial infections	Marker of bacterial load and systemic infection severity	Not suppressed by GCs, enabling ongoing infection monitoring	Priming and modulatory; guides antibiotic use and tracks bacterial clearance
D-dimer	A fibrin degradation product indicating clot formation and breakdown	Reflects coagulopathy and thromboinflammatory activation	Indirectly reduced via inflammation control and endothelial stabilization	Priming and modulatory; elevated levels predict MODS and guide anticoagulation strategies
Ferritin	An iron-storage protein and acute-phase reactant	Correlates with macrophage activation, tissue damage, and inflammation severity	Declines gradually during recovery; prolonged elevation suggests immune dysregulation	Modulatory and restorative; used for risk stratification and tracking resolution
Lactate[a]	A metabolic byproduct of anaerobic glycolysis	Indicates tissue hypoperfusion and mitochondrial dysfunction	GCs support mitochondrial function, aiding lactate clearance	Priming; high lactate predicts mortality, and clearance indicates improved perfusion
Mitochondrial DNA (mtDNA) [emerging]	Cell-free DNA released from damaged mitochondria	Acts as a DAMP, triggering innate immune activation	Reduction reflects improved mitochondrial integrity and decreased cellular stress	Priming; early predictor of severity and organ failure risk; still under investigation
TOS/TAC ratio [emerging]	Total oxidant status (TOS) and total antioxidant capacity (TAC) reflect systemic redox balance	Indicates oxidative stress burden vs. antioxidant defense during inflammation	GCs indirectly improve TAC by reducing oxidative burden and supporting mitochondrial recovery	Modulatory; emerging biomarker to assess redox homeostasis and identify delayed recovery. Clinical utility under investigation
HDAC2 (histone deacetylase 2) [emerging]	An enzyme that modulates chromatin structure and regulates inflammatory gene transcription	Critical for repressing pro-inflammatory gene expression via GRα transcriptional activity	GCs restore HDAC2 function, enabling resolution of inflammation. Dysfunction impairs GC efficacy	Modulatory; emerging marker of steroid responsiveness, especially in redox-impaired states. Needs clinical validation
Annexin A1	A GC-inducible protein that mediates inflammation resolution via neutrophil regulation and efferocytosis	Facilitates termination of inflammation and promotes tissue healing	Upregulated via GC signaling; mimics steroid effects on immune modulation and vascular stability	Restorative; promising marker of inflammation resolution and target for GC-sparing strategies
DUSP1 (dual-specificity phosphatase 1)	A phosphatase that deactivates MAPKs, regulating inflammatory signaling	Shuts down cytokine cascades, supporting transition to immune resolution	Rapidly induced by GC exposure; mediates suppression of IL-6, TNF-α, and MAPK pathways	Modulatory; early marker of GRα transcriptional activation. Promising intracellular readout of GC efficacy

Table 4 (*Continued*)

Biomarker	Definition	Pathophysiologic role	GC impact	Phase and clinical interpretation
GILZ (glucocorticoid-induced leucine zipper)	A GC-responsive gene product that modulates inflammation and immune responses	Inhibits transcription factors like NF-κB and AP-1; promotes anti-inflammatory signaling and immune resolution	Rapidly upregulated by GCs; contributes to suppression of cytokine production and immune cell activation	Modulatory; intracellular marker of GC transcriptional activation. Potential surrogate of GRα pathway engagement in early response

Abbreviations: ACTH, adrenocorticotropic hormone; annexin A1, annexin a1 protein; CRP, C-reactive protein; DAMP, danger-associated molecular pattern; DUSP1, dual-specificity phosphatase 1; GC, glucocorticoid; GILZ, glucocorticoid-induced leucine zipper; GR, glucocorticoid receptor; FKBP5, FK506-binding protein 5; HDAC2, histone deacetylase 2; HPA, hypothalamic–pituitary–adrenal; ICU, intensive care unit; IL-6, interleukin-6; mtDNA, mitochondrial DNA; NLRP, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; TAC, total antioxidant capacity; TOS, total oxidative status.

Note: This table outlines key biomarkers for evaluating biological stress responses and the progression of homeostatic correction in critically ill patients. Biomarkers are categorized by their predominant relevance within one of three sequential phases—priming, modulatory, and restorative. Each biomarker provides diagnostic, prognostic, or therapeutic insight into systemic inflammation, immune recalibration, oxidative stress, mitochondrial integrity, tissue repair, or endocrine adaptation. Several biomarkers span multiple phases, reflecting the dynamic transitions and regulatory feedback loops that characterize glucocorticoid-responsive physiology. The "Phase and Clinical Interpretation" column highlights where each biomarker offers the most clinical or mechanistic utility. Emerging biomarkers—including HDAC2, GILZ, Annexin A1, DUSP1, and TOS/TAC ratio—are supported by preclinical or translational data with promising diagnostic and therapeutic relevance. However, these remain under active investigation and are not yet validated for routine clinical use. Full mechanistic details and supporting references are provided in **Appendix 2** (available in the online version only). Emerging biomarkers are those supported by preclinical or translational data with promising diagnostic or therapeutic implications, but remain under active investigation and have not yet been fully validated for routine clinical use.

[a]Lactate elevation reflects impaired cellular metabolism and may result from (1) inadequate oxygen delivery (e.g., shock, sepsis) triggering anaerobic glycolysis; (2) mitochondrial dysfunction limiting oxidative phosphorylation despite adequate oxygen; and (3) adrenergic stimulation enhancing glycolytic flux. Clinical research only.

Modulatory Phase: Overview and Biomarker Applications

As outlined in **Table 4**, biomarkers shift during the modulatory phase, where the therapeutic emphasis transitions to suppressing hyperinflammation, restoring redox balance, and stabilizing vascular function. Central biomarkers in this phase include procalcitonin (PCT), histone deacetylase 2 (HDAC2), and total oxidant/antioxidant capacity (TOS/TAC) ratios, which together reflect progressive resolution of inflammation and improvement in systemic homeostasis.[102,103]

Accompanying this shift is a progressive decline in IL-6, CRP, and PCT levels coupled with improvements in redox balance and endothelial function. mtDNA, although predominantly relevant to the priming phase, may exhibit gradual resolution, signaling recovery from mitochondrial injury. Restoration of TOS/TAC and HDAC2 activity is indicative of improved redox homeostasis and reactivation of GRα-mediated anti-inflammatory transcriptional pathways.

New markers, such as HDAC2 and TOS/TAC, help us understand two key aspects: how genes are switched on or off (epigenetics) and how effectively the body manages oxidative stress. In patients with persistent or slowly resolving inflammation, these markers can help identify those who might benefit from antioxidant support or treatments that assist in resetting gene function activity.[102,103]

Moreover, intracellular signaling molecules like glucocorticoid-induced leucine zipper (GILZ)[146] and dual-specificity phosphatase 1 (DUSP1)[147,148] serve as direct indicators of GRα activation. The rapid induction of GILZ inhibits NF-κB and AP-1, thereby limiting neutrophil activation and promoting immune resolution.[146] DUSP1 deactivates MAPK pathways (ERK, JNK, p38), reducing cytokine release and downstream pro-inflammatory responses.[147,148] While both genes are upregulated early, within 1 to 2 hours of GC exposure,[149,150] their primary role is to resolve inflammation, not to initiate immune priming. This GRα-driven transcriptional response, marked by the early induction of genes like DUSP1 and GILZ, is a fundamental mechanism in molecular pharmacology through which GCs suppress MAPK-dependent cytokines and promote the resolution of inflammation.[151,152] This was confirmed in DUSP1$^{-/-}$ mouse models, where dexamethasone failed to inhibit MAPK activity or suppress inflammatory cytokines, confirming DUSP1 as a key mediator of GC efficacy in both in vitro and in vivo studies.[153]

Restorative Phase: Overview and Biomarker Applications

In the restorative phase, the therapeutic focus shifts to resolving inflammation, clearing dead cells and debris, supporting tissue repair, maintaining organ integrity, and re-establishing adaptive immunity. Biomarker patterns during this phase show sustained reductions in inflammatory cytokines, normalization of vascular integrity markers, and signs of restored tissue homeostasis. This phase involves reprogramming immune cells, especially the transition of macrophages toward a pro-resolving phenotype and the suppression of residual innate immune signaling. Key biomarkers, such as increasing Annexin A1 and decreasing ferritin, indicate this progression.

Annexin A1 is a GC-inducible protein that plays a key role in orchestrating resolution during this phase. Its upregulation signifies successful activation of GRα-mediated resolution pathways. Functionally, Annexin A1 ends inflammation by inhibiting neutrophil infiltration, promoting efferocytosis (the clearance of apoptotic cells by phagocytes), and suppressing the production of pro-inflammatory mediators. In this context, resolution refers to

the active removal of inflammatory debris and the start of tissue repair after earlier inflammation damage.[154–156] These effects are mediated through Annexin A1's binding to formyl peptide receptor 2 (FPR2), which activates pro-resolving signaling cascades that end inflammation without impairing host defenses.[157,158]

GCs increase Annexin A1 expression through both genomic and nongenomic mechanisms involving the GR, as well as PI3K, PKC, and MAPK signaling pathways. Once phosphorylated, Annexin A1 moves to the cell membrane, where it exerts its anti-inflammatory and pro-resolving functions.[159,160] Clinically, Annexin A1 serves as a molecular marker of GC effectiveness in restoring immune balance. Its expression indicates progress toward resolving inflammation and suggests that homeostatic correction is nearly finished. Notably, experimental therapies involving Annexin A1 mimetics or FPR2 agonists seem promising as GC-sparing agents, maintaining pro-resolving effects while reducing treatment-related side effects.[161,162] Declining ferritin levels during the restorative phase, discussed in detail in **Supplementary Appendix 2** (available in the online version only), serve as a reliable indicator of immune resolution and macrophage reprogramming. When analyzed alongside CRP and IL-6, a sustained downward trend signals a shift toward immune resolution and supports reducing the GC dose. In contrast, persistent elevation may indicate unresolved immune activation or progression toward macrophage activation syndromes.

A brief overview of multi-omic approaches in critical illness is provided in **Supplementary Appendix 2** (available in the online version only).

Evolving Outcome Priorities in Glucocorticoid Trials

A critical limitation of previous GC trials lies in their predominant use of mortality as the primary outcome measure, which often fails to capture the underlying mechanisms of therapeutic failure. As widely acknowledged in critical care research, mortality represents a crude and highly confounded endpoint, influenced by a multitude of factors unrelated to the intervention itself. These include baseline disease severity, comorbidities, patient age, frailty, and individual care preferences (e.g., do-not-resuscitate orders).[163–165]

This issue is particularly pertinent in GC trials, where therapeutic efficacy is intricately linked to the appropriateness of timing, dosing, treatment duration, and alignment with the patient's underlying immune phase and GC receptor functionality. When clinical protocols fail to account for fundamental pathobiological mechanisms or essential pharmacological principles—such as optimal treatment windows, individualized dosing strategies, adequate duration of therapy, or patient stratification based on immune status—ineffectiveness is frequently misattributed to the intervention itself rather than methodological shortcomings in study design.[5,166,167] In the absence of biomarker-guided monitoring or mechanistic outcome measures, clinical trials are at risk of incorrectly concluding that a treatment is ineffective when, in fact, the failure may be due to suboptimal treatment protocols, leading to the premature rejection of potentially beneficial therapies. **Table 5** outlines key methodological flaws that have historically limited the accurate interpretation of GC trial outcomes in critical illness.

AI and the Data-Wealthy Intensive Care

Among clinical environments, the ICU stands out as uniquely suited for AI applications, due to its wealth of continuously monitored physiological parameters, extensive laboratory data, and rich imaging resources. Persistent challenges, such as early disease detection, optimization of treatment strategies based on pharmacological principles, and a pathobiological understanding of disease mechanisms, remain crucial areas where AI applications can offer significant improvements. A useful framework for conceptualizing AI, or more broadly, "Data Science" as an umbrella term for all data analysis types, classifies tasks according to the scientific questions they address: description, prediction, and causal inference.[168] Descriptive tasks, which may or may not involve AI models, are fundamentally distinct from prediction and causal inference as they do not require inferences about a patient's future state or response to interventions. Instead, they involve transforming raw data into improved insights through visualization or summarization (such as patient conversations 2).[169] These tasks likely provide the quickest way to enhance ICU care, as they don't require the development and validation of complex models. Their deployment is also considered less risky because they do not directly influence medical decisions. Examples include visualizing daily cortisol levels and GR expression trends or summarizing the frequency of specific corticosteroid tapering strategies, which are descriptive. Another example includes monitoring dynamic patterns of GC responsiveness using biomarker panels. (e.g., CRP, IL-6, and GCRα expression) to visualize transitions through priming, modulatory, and restorative phases (see section "Phase-Specific Biomarkers for Monitoring Homeostatic Correction").

Prediction tasks, on the other hand, forecast future patient states, allowing clinicians to make more informed decisions. For example, predicting which patients are likely to develop steroid-induced hyperglycemia based on their baseline characteristics or estimating the risk of adrenal insufficiency after corticosteroid withdrawal can inform clinical management. We may refer to AI models trained for such prediction tasks as Predictive AI models.[170] Incorporating predictors of GC resistance—such as low GRα expression, elevated FKBP5, or MAPK pathway activation (**Table 3**)—could improve the predictive accuracy of AI models and help identify patients unlikely to benefit from standard corticosteroid treatments. However, identifying patients with a poor prognosis is fundamentally different from deciding the best way to prevent an adverse outcome or treat a disease. While factors like high heart rate or vasopressor infusions may both be strong predictors of ICU mortality, it is not necessarily reasonable to assume that administering β-blockers or stopping vasopressors would lower the patient's risk of death.[171,172] For an AI to advise clinicians on prevention or treatment, it must predict how actions (or treatments) will affect future outcomes. This task is called causal inference and is distinct from other types of predictions.[173,174] Causal inference involves estimating the causal effect of a specific intervention or treatment on an outcome. Accurate predictions of treatment effects for groups or individuals, if properly validated, can help ICU physicians make more informed treatment choices, such as evaluating the average effect of various ventilation strategies (e.g., higher vs. lower PEEP)[175,176] in ARDS or personalizing these choices for individual patients.[177] It is

Table 5 Systemic limitations undermining current RCT designs for glucocorticoid therapy in critical illness

Limitation	Description	Impact on interpretation and outcomes
Fixed dose and duration	Uniform regimens (e.g., 7–10 d) applied regardless of illness trajectory, severity, or response	Masks a therapeutic signal; increases risk of underdosing in resistant states and overtreatment in recovery
Lack of temporal stratification	Interventions not aligned with dynamic illness phases: priming, modulatory, and restorative	Creates a mismatch between drug action and biological readiness; reduces efficacy and obscures benefit
Absence of early biomarker-based entry criteria	Patients are enrolled based on clinical diagnosis alone, without an inflammatory threshold (e.g., CRP > 150–200 mg/L)	Includes biologically noninflamed patients unlikely to benefit; dilutes signal and reduces trial power
Unphysiological mode of administration	GC administration often lacks alignment with natural cortisol dynamics. Continuous infusion without a bolus fails to replicate stress physiology	May delay receptor engagement and hemodynamic response; distorts efficacy signals compared to bolus or bolus + infusion regimens
Absence of response-guided titration	No adaptive adjustment based on clinical course or biomarker feedback	Limits individualization; fosters therapeutic inertia or premature withdrawal despite ongoing need
Limited biomarker integration	Biomarkers (CRP, IL-6, lactate, ferritin, D-dimer, PCT) are underutilized in trial design and monitoring	Weakens risk stratification; delays recognition of responders; undermines mechanistic outcome validation
Inadequate tapering strategies	Glucocorticoids are often discontinued abruptly without physiological weaning	Provokes rebound inflammation, delayed recovery, or HPA suppression—potentially misread as treatment harm
Failure to monitor for adrenal insufficiency	RCTs rarely assess HPA axis recovery or test adrenal function (e.g., ACTH stimulation) before discharge	Misses diagnosis of secondary adrenal insufficiency; increases risk of postdischarge complications and misclassification of treatment failure
Oversimplified pharmacologic framing	GCs are viewed primarily as anti-inflammatories, neglecting endocrine and homeostatic functions	Undervalues roles in metabolic regulation, mitochondrial preservation, and vascular stability
Exclusion of adjunctive co-interventions	Trials omit micronutrients, antioxidants, or probiotics that enhance GRα function	Underestimates the benefit of synergistic therapies; limits real-world relevance of trial outcomes
Delayed initiation of therapy	GCs are initiated after advanced organ damage or immune exhaustion is established	Misses the optimal window for efficacy; treatment appears ineffective due to biological nonresponsiveness
Inadequate patient phenotyping	Trials include heterogeneous populations without immune or inflammatory profiling	Obscures subgroup-specific effects; dilutes treatment signal and impairs outcome interpretation

Abbreviations: ACTH, adrenocorticotropic hormone; AI, artificial intelligence; ARDS, acute respiratory distress syndrome; CRH, corticotropin-releasing hormone; CRP, C-reactive protein; DAMPs damage-associated molecular patterns; DEX, dexamethasone; DNA, deoxyribonucleic acid; GC, glucocorticoid; GR, glucocorticoid receptor; GRα, glucocorticoid receptor alpha; HPA, hypothalamic-pituitary-adrenal; ICU, intensive care unit; IL, interleukin; IL-6, interleukin-6; IL-10, interleukin-10; LPS, lipopolysaccharide; MAS, macrophage activation syndrome; MDW, monocyte distribution width; mtDNA, mitochondrial DNA; PAMPs, pathogen-associated molecular patterns; PCT procalcitonin; PRR, pattern recognition receptor; RCT, randomized controlled trial; sHLH, secondary hemophagocytic lymphohistiocytosis; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.
Note: The table outlines key conceptual and methodological flaws that have historically limited the detection of treatment benefit in RCTs evaluating glucocorticoids in critical illness. These include failure to stratify patients by biological readiness, delayed therapy initiation, lack of response-guided titration, omission of tapering, and disregard for the dynamic endocrine role of GC–GRα signaling. Collectively, these limitations confound interpretation and risk discarding beneficial treatments.

common to refer to AI models trained for causal inference tasks as "Actionable AI."[170]

Toward More Personalized Treatment with AI

Among various clinical settings, the ICU provides a particularly promising environment for studying heterogeneity of treatment effects (HTE).[178,179] A widely hypothesized explanation for the poor track record of many ICU RCTs is that many interventions fail to show significant mortality reduction,[180] is the inherent heterogeneity of the ICU patient population. Unlike well-defined conditions, many ICU systemic diseases like ARDS have highly diverse etiologies. This patient variability can lead to a wide range of responses to different treatments, with some patients benefiting, others seeing no effect, and some possibly being harmed, ultimately resulting in neutral overall trial outcomes.

GC therapy exemplifies this challenge. Despite consistent physiological benefits, such as reducing inflammation and enhancing oxygenation, treatment outcomes vary significantly due to unpredictable factors, including differences in receptor sensitivity and GC plasma levels that influence GR saturation, as well as study protocols that do not align with pharmacological principles. Identifying and validating HTE in GC therapy is therefore crucial for improving outcomes in conditions such as sepsis, ARDS, and severe pneumonia.

Traditionally, HTE is studied through "one-variable-at-a-time" subgroup analyses, where subgroups are defined based on characteristics and cut-offs chosen according to domain knowledge or data availability.[181,182] There are well-known limitations to this approach, including that individual trials are often statistically underpowered to test interactions, which can lead to false-negative results, and the risk of false-positive findings when multiple subgroup analyses are performed. While measures like conducting larger trials, subgroup prespecification, and adjustments for multiplicity can address these issues, a major limitation of

traditional subgroup analysis remains: patients often belong to multiple overlapping subgroups, which may experience treatment effects of varying magnitude and direction.[179,183] To overcome these limitations, Predictive HTE analyses utilize multivariable models to evaluate variation across multiple patient characteristics simultaneously.[179,184,185] These methods are divided into two main categories: risk modeling and effect modeling. Risk models categorize patients based on predicted risk using covariates and outcomes, regardless of treatment assignment, and detect HTE through the risk-magnification phenomenon, where consistent relative effects result in larger absolute benefits in higher-risk groups of individuals.[186,187] Effect models, on the other hand, incorporate treatment assignments during training to directly model treatment–covariate interactions and estimate individualized treatment effects; while they are theoretically ideal for HTE detection, they are prone to overfitting.[179,184]

A specific example of this is the controversy surrounding the routine use of corticosteroids for patients hospitalized with CAP, with current treatment guidelines often conflicting.[188,189] The hypothesis that patients with severe CAP benefit more from corticosteroids is problematic because there are many different definitions of severe CAP, and it is based on comparisons between, rather than within trials.[190,191] Smit et al[136] used a data-driven approach to develop and externally validate a corticosteroid-effect model to predict the benefit from adjuvant corticosteroid therapy, which identified baseline CRP as a key modifier of effect. Their results showed a significant reduction in overall mortality among all included CAP patients who received adjuvant corticosteroid therapy. Importantly, this treatment effect varied notably between subgroups identified by the corticosteroid-effect model: patients with high baseline CRP levels gained a survival benefit, while those with low baseline CRP levels did not. Remarkably, no significant HTE was observed between less severe and severe CAP (regardless of the severity definition used), directly challenging the current severity-based approach. This analysis clearly demonstrates that baseline CRP is a strong predictor of corticosteroid response, marking a significant step toward more personalized corticosteroid treatment. In the growing field of AI-driven HTE analyses, there are many other recent models developed for ICU treatments, such as oxygen targets,[192] or heparin administration,[193] which could lead to more personalized treatment decisions for critically ill patients.

Beyond CAP, predictive HTE models could be used for other critical illnesses that respond to GCs. For example, in ARDS, detecting responders through early changes in oxygenation index, vasopressor requirements, or neutrophil transcriptomic signatures might help customize corticosteroid doses. Similarly, in septic shock, modeling how mineralocorticoid co-activation interacts with GRα expression could allow for patient-specific adjustments to improve hemodynamic recovery and reduce ICU stay.

Remaining challenges in HTE analysis include balancing accuracy with the risk of overfitting when using effect modeling, evaluating predictive performance based on effects rather than just outcomes, and assessing the reliability of HTE findings to guide medical treatment decisions. Due to the highly diverse nature of ICU patients, many other ICU treatments likely also exhibit significant HTE. Therefore, AI-driven HTE analyses provide significant potential for customizing a wide range of ICU therapies, including GC-based treatments. Future AI applications may also facilitate phase-specific modeling of GC action, dynamically adjusting dose and duration based on transition points between pro-inflammatory, resolving, and reparative stages of illness.

Taken together, AI serves as a powerful complement to traditional clinical decision-making frameworks, supporting a precision medicine approach that responds to the individual trajectory and biological heterogeneity of critically ill patients. AI-driven, biomarker-guided research protocols represent a new frontier in critical care therapeutics. They enable dynamic learning, enhance patient stratification, and facilitate targeted interventions, while overcoming many of the design limitations that have historically constrained GC trials. Future research should focus on prospective validation, ethical integration, and the development of transparent, clinician-augmented AI tools to support phase-specific modeling, personalized GC dosing and tapering strategies, and the real-time identification of treatment responders versus nonresponders.

This integrated progression enables dynamic and proportionate responses to severe physiological stress, promoting the recovery of systemic homeostasis.[2]

Conclusion

GCs remain a cornerstone of critical care; however, conventional one-size-fits-all protocols have likely constrained their full therapeutic potential. GC-GRα signaling extends beyond anti-inflammatory effects, acting as a dynamic regulator of adaptive homeostasis across the priming, modulatory, and restorative phases of illness.

Realizing the full benefits of GC therapy may depend on transitioning toward precision-based, phase-specific, and biomarker-guided strategies tailored to the patient's evolving physiological state. **Table 6** presents best practice recommendations for optimizing GC therapy. Future clinical research could benefit from moving beyond binary outcomes, such as mortality, and instead exploring biologically grounded outcomes, including the timing of intervention within reversible phases, measurable biological responses (e.g., reductions in CRP or IL-6, improved oxygenation, decreased vasopressor requirements), and effective tapering strategies aligned with biomarker trajectories and adrenal axis recovery. In addition to measuring clinical outcomes, a key objective should be to determine whether treatment effectively engages its biological targets and sustains that engagement over time. Adaptive treatment designs—accounting for patient heterogeneity, changing disease dynamics, and real-time biomarker feedback—may offer a more accurate framework for evaluating treatment efficacy.

A comprehensive review of the key factors influencing GC treatment responses and mechanism-based strategies to overcome resistance is provided in Chapter 3.[1] This includes a detailed discussion of GRα/GRβ isoform balance, pharmacokinetic variability, receptor saturation, mitochondrial dysfunction, redox imbalance, and endocrine disruption. The conceptual framework outlined in Chapter 3 provides a blueprint for restoring GRα function across diverse clinical settings and developing individualized, response-guided protocols tailored to the evolving needs of patients.

Table 6 Response-guided principles for glucocorticoid therapy in critical illness

Protocol element	Best practices for optimizing GC efficacy
Initiation timing	Start GC therapy within 24–48 h of illness onset to prevent irreversible immune and organ damage. Initiation within this window maximizes the therapeutic window before receptor dysfunction and metabolic collapse. Earlier initiation is recommended in patients already requiring vasopressors or mechanical ventilation
Loading dose[a]	Administer an initial bolus of approximately 80–100 mg of methylprednisolone, equivalent to rapidly achieve GRα receptor saturation and initiate both genomic and nongenomic signaling. The loading dose compensates for the expanded volume of distribution and delays in receptor occupancy under stress conditions
Infusion strategy	Follow the bolus with continuous infusion (administering the same dose over 24 h) to maintain steady plasma concentrations, enhance tissue penetration, and prevent receptor desaturation. This approach sustains prolonged GR engagement and reduces pharmacokinetic fluctuations
Adjunctive strategies[b]	Support GC efficacy by administering key micronutrients (vitamins C, D, Thiamine, zinc, selenium), melatonin, and probiotics. These agents enhance GRα function by reducing oxidative stress, restoring mitochondrial activity, and stabilizing epithelial barriers. Melatonin protects GR structure and HDAC2 from oxidative inactivation, while probiotics reinforce gut and immune homeostasis
Monitoring response[c]	Monitor the daily clinical trajectory alongside key biomarker trends to assess treatment response. A CRP reduction of $\geq$ 50% within 48 h is generally expected and serves as an early indicator of glucocorticoid effectiveness. If this response is delayed or absent, consider the possibility of early treatment resistance and promptly reevaluate dosing, route of administration, or the need for adjunctive interventions. Biomarkers such as CRP, IL-6, lactate, D-dimer, procalcitonin (PCT), ferritin, and neutrophil-to-lymphocyte ratio (NLR) provide complementary insights into GRα activation, inflammatory resolution, and tissue recovery
Nonresponse at 48–72 h, or earlier clinical worsening	Escalate therapy if there is no improvement within 48–72 h, or earlier if clinical deterioration occurs. Increase the dose by 50–100%, rebolus, and raise the daily infusion rate to ensure re-saturation of GRα receptors. Consider adjunctive strategies that target inflammatory pathway interference, mitochondrial dysfunction, or unresolved micronutrient deficiencies. This adaptive approach helps prevent treatment failure due to insufficient receptor activation or the emergence of glucocorticoid resistance
Initial treatment duration	Maintain the full glucocorticoid dose for at least 2–4 d after withdrawal of life-supporting interventions (e.g., mechanical ventilation, vasopressors, or renal replacement therapy) to support continued resolution of inflammation, facilitate mitochondrial recovery, and promote tissue stabilization
Treatment de-escalation	Initiate the first dose reduction only after the patient demonstrates sustained clinical stability and consistent improvement in biomarkers of inflammation. Premature dose reduction or discontinuation may trigger rebound inflammation, disrupt immune recovery, and increase the risk of adverse outcomes, including mortality. The duration of treatment de-escalation is variable (4–8 d) and should be guided by the patient's clinical trajectory, biomarker trends, and the prior duration and intensity of glucocorticoid therapy
Tapering[d]	Taper slowly over 6–8 d after both clinical and biomarker stability are achieved and the patient has completed the treatment de-escalation phase. Begin tapering only when recovery is sustained, and there is no evidence of inflammatory rebound or hemodynamic instability. Reduce the dose by approximately 10–20% every 1–2 d, adjusting based on prior treatment duration, illness severity, and patient tolerance. Premature tapering or abrupt discontinuation may result in rebound inflammation, adrenal insufficiency, immune dysregulation, and increased mortality. Monitor inflammatory markers—such as CRP and PCT—during and after tapering to detect early signs of inflammatory rebound and guide timely re-escalation or supportive interventions
Route transition	Switch to oral GC only after at least 5 d following withdrawal of life-supporting interventions, when GI absorption improves. Premature switch risks underexposure. Monitor clinical and biomarker stability to guide transition timing

Abbreviations: CRP, C-reactive protein; DAMP, damage-associated molecular pattern; GC, glucocorticoid; GI, gastrointestinal; GRα, glucocorticoid receptor alpha; HDAC2, histone deacetylase 2; IL-6, interleukin-6; mtDNA, mitochondrial DNA; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; RRT, renal replacement therapy.

Note: **Table 5** outlines a suggested response-guided framework for glucocorticoid therapy in critical illness, synthesizing pharmacologic principles with dynamic clinical markers. While not intended as a rigid protocol, it serves as a flexible, evidence-informed guide to optimize GC efficacy based on individual patient trajectories and treatment responses. Although the focus is on GC therapy, it also underscores the importance of phase-specific adjunctive strategies, including micronutrient and probiotic support, particularly in the absence of standardized ICU protocols. These approaches, while promising, must be validated not only through prospective, biomarker-stratified randomized controlled trials but also via complementary methodologies such as real-world evidence studies, adaptive platform trials, mechanistic translational research, and AI-assisted modeling to ensure safety, efficacy, and clinical applicability.

[a]Methylprednisolone 80 to 100 mg, approximately hydrocortisone 400 to 500 mg, approximately dexamethasone 15 to 18.75 mg.

[b]Following the recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN), micronutrients should be administered early and in adequate amounts to correct deficiencies, support mitochondrial function, and modulate inflammatory responses in critically ill patients.[86,87]

[c]Key biomarkers: CRP, IL-6, D-dimer, lactate, mtDNA, TOS/TAC, HDAC2, DUSP1, Annexin A1, GILZ, PCT.

Ultimately, this reframing supports a transition to a precision medicine model, one in which GC therapy is aligned with the illness phase, guided by dynamic biomarkers, and optimized through co-interventions. Achieving this will require integrative platforms—potentially powered by AI—that synthesize clinical, biological, and temporal signals into actionable decision-support tools.

Such an individualized, multimodal treatment paradigm offers a coherent and potentially more effective strategy for restoring

homeostasis, minimizing treatment-related harm, and improving patient outcomes in critical illness.

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Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

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Note A comprehensive literature review was conducted using Google Scholar and the Consensus database to identify relevant articles published between 1995 and 2025. Manual screening of references from key review articles and clinical guidelines was also performed to ensure completeness and relevance to this translational synthesis.

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