



## Review

# Glucocorticoid therapy for acute respiratory distress syndrome: Current concepts



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## ABSTRACT

Acute respiratory distress syndrome (ARDS), a fatal critical disease, is induced by various insults. ARDS represents a major global public health burden, and the management of ARDS continues to challenge healthcare systems globally, especially during the pandemic of the coronavirus disease 2019 (COVID-19). There remains no confirmed specific pharmacotherapy for ARDS, despite advances in understanding its pathophysiology. Debate continues about the potential role of glucocorticoids (GCs) as a promising ARDS clinical therapy. Questions regarding GC agent, dose, and duration in patients with ARDS need to be answered, because of substantial variations in GC administration regimens across studies. ARDS heterogeneity likely affects the therapeutic actions of exogenous GCs. This review includes progress in determining the GC mechanisms of action and clinical applications in ARDS, especially during the COVID-19 pandemic.

## Introduction

Acute respiratory distress syndrome (ARDS), a common clinical syndrome of acute respiratory failure, is characterized by refractory hypoxemia with bilateral infiltrates on chest imaging, which cannot be explained by acute cardiac failure or fluid overload.<sup>[1,2]</sup> Supportive treatments including lung-protective ventilation, prone position ventilation, and restrictive fluid infusion improve the outcomes of ARDS. However, no specific drug has been found effective in its treatment.<sup>[3]</sup> Because of their obvious anti-inflammatory role, glucocorticoids (GCs) have been used to treat ARDS for decades, especially during the Coronavirus disease 2019 (COVID-19) pandemic, though their pharmacologic mechanisms of action on ARDS remain unclear. Herein, we first review the ARDS definition, etiology, epidemiology, and pathophysiology. We then discuss the effects and mechanisms by which GCs affect ARDS, and how ARDS heterogeneity affects GC actions. Finally, we address the side effects of GCs.

## ARDS Definition, Epidemiology, Etiology, and Pathophysiology

## Definition

The definition of ARDS has undergone four versions since it was first published in 1967. Because the COVID-19 pandemic emphasized the importance of expanding its definition, the global definition published in 2023 expanded the Berlin definition, to provide a more feasible diagnosis, especially in resource-limited areas.<sup>[4]</sup>

An important modification in the newest definition is the inclusion of treatment with high flow nasal oxygen >30 L/min without required partial pressure of oxygen in arterial blood (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>), positive end-expiratory pressure. Many patients with mild hypoxemia or rapidly improving ARDS are thus now eligible for inclusion in clinical trials, substantially changing epidemiological estimates

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of ARDS incidence and misclassification of ARDS severity and diagnosis.<sup>[5]</sup> Another major change is the criteria for hypoxemia, with the recommendation to use peripheral oxygen saturation (SpO<sub>2</sub>)/FiO<sub>2</sub> to diagnose ARDS when SpO<sub>2</sub> ≤97 % and blood gas is unavailable, instead of PaO<sub>2</sub>/FiO<sub>2</sub>. The advantage of this is that SpO<sub>2</sub>/FiO<sub>2</sub> can be measured continuously, non-invasively, and with high sensitivity. However, the validity of SpO<sub>2</sub>/FiO<sub>2</sub> as an alternative to PaO<sub>2</sub>/FiO<sub>2</sub> remains controversial, especially considering evidence of racial bias and high-dose vasopressor use.<sup>[6,7]</sup> The new definition also recommends lung ultrasound (LUS) as an alternative for detecting bilateral (non-cardiogenic) filtration, especially when chest radiography/computed tomography (CT) is unavailable. However, the lack of clear rules for using LUS in ARDS diagnosis is a major flaw of the current definition, and it may lead to ARDS misclassification.

ARDS is a clinical syndrome, rather than a disease. The global definition is not “new,” but rather an expansion of the Berlin definition to meet the current situation. Indeed, there may not be a “best” ARDS definition. Rather, we must assess the definition’s reliability and validity across settings and patient groups to provide “better” diagnostic criteria.<sup>[8]</sup>

### Epidemiology

Despite significant progress in understanding its pathogenesis and the use of supportive therapies, the incidence of ARDS remains high, especially in resource-restrained regions. It occurs in approximately 10% of patients in the intensive care unit (ICU) and 23% of those who are ventilated<sup>[9]</sup> with morbidity increases from 30% to 52% during the COVID-19 pandemic.<sup>[10]</sup> There is a significant increase in mortality with each increase in ARDS severity category, with 34.9% for mild, 40.3% for moderate, and 46.1% for severe ARDS.<sup>[9,11]</sup>

### Etiology

ARDS can be caused by various factors including, but not restricted, to pneumonia, sepsis, pancreatitis, aspiration of gastric contents, severe trauma and burns, and smoke inhalation.<sup>[2]</sup> E-cigarette and vaping product use-associated lung injury<sup>[12]</sup> and COVID-19<sup>[13]</sup> have also emerged as new causes of ARDS. In recent studies, sepsis, pneumonia, and aspiration of gastric contents together accounted for >85 % of ARDS cases.<sup>[9,14–17]</sup> (The known causes of ARDS are shown in [Table 1](#).)

### Pathophysiology

ARDS is an acute inflammatory syndrome of the alveoli and capillaries, characterized by alveolar epithelium and capillary endothelial injury with subsequent inflammatory exudation from alveolar capillaries.<sup>[18]</sup> Direct and indirect insults damage the alveolar structure and microvasculature ([Figure 1A](#)). Damage to the endothelial–epithelial barrier is essential in the development of ARDS, which leads to intra-alveolar and interstitial edema due to increased capillary permeability.

### Exudative phase

In the exudative phase, the activated alveolar resident macrophages release proinflammatory mediators, leading to the accumulation of neutrophils, monocytes, and effector T

**Table 1**  
Causes of acute respiratory distress syndrome.

Pulmonary (direct)	Non-/extra-pulmonary (indirect)
Pneumonia <ul style="list-style-type: none"> <li>• Bacterial</li> <li>• Viral</li> <li>• Fungal</li> <li>• Opportunistic</li> </ul>	Non-pulmonary sepsis <ul style="list-style-type: none"> <li>• Abdominal</li> <li>• Urinary</li> <li>• Bloodstream</li> <li>• Others</li> </ul>
Near drowning Aspiration of gastric contents Ventilation-associated injury Inhalation injury	Pancreatitis Severe traumatic injury Severe burn injury Drug toxicity Neurogenic Transfusion of blood products Radiation pneumonitis Cardiopulmonary bypass Ischemia-reperfusion injury after transplantation

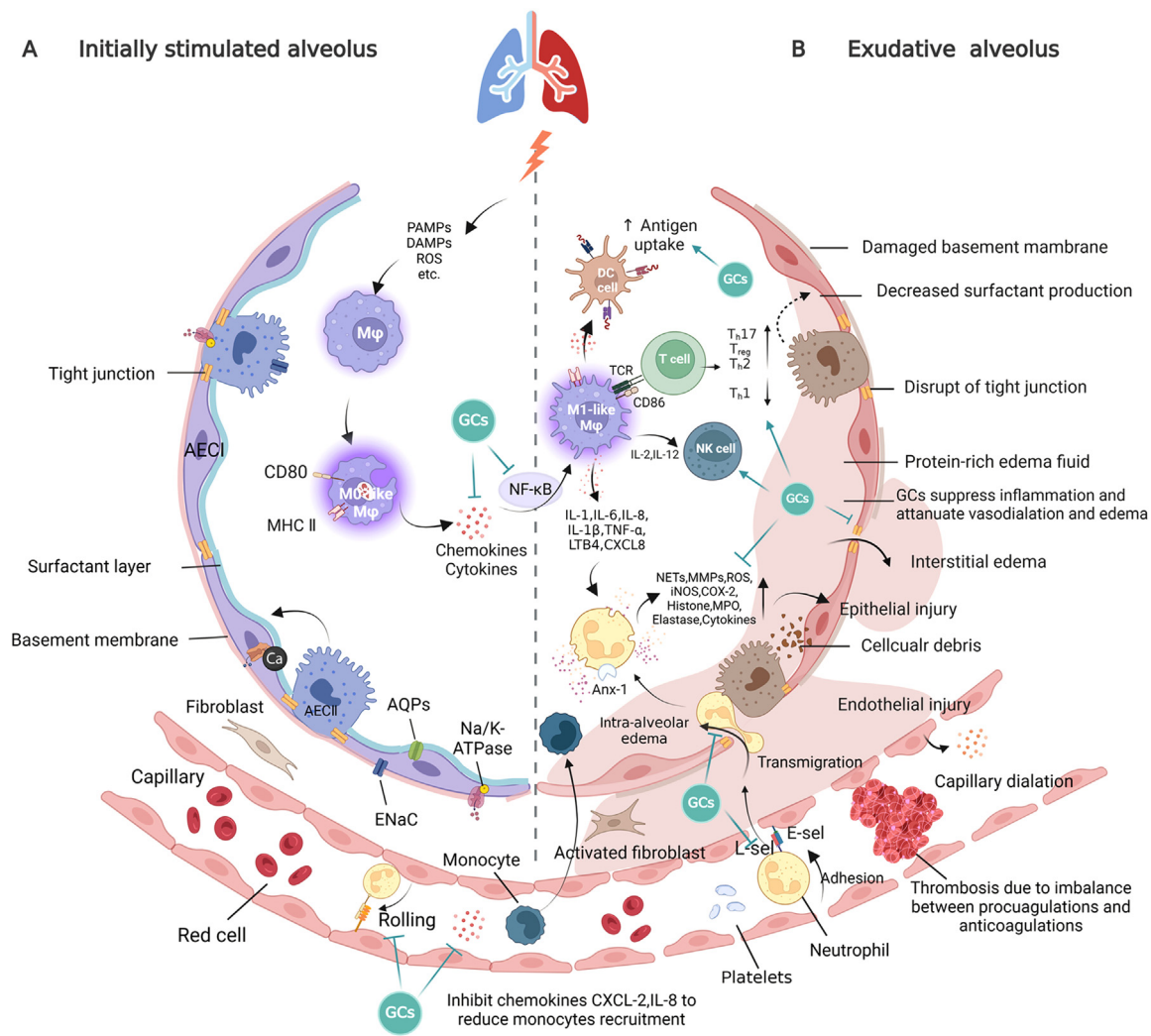
cells.<sup>[19]</sup> Recruitment of neutrophils to the lung is a key step in the pathogenesis of ARDS.<sup>[20]</sup> Proinflammatory mediators, mostly interleukin-8 (IL-8), released from either alveolar resident macrophage or activated intravascular immune cells, cause neutrophils to be primed, adhered, and then crossover the capillary wall into the interstitium and alveoli, releasing reactive oxygen species (ROS), antimicrobial peptides, proinflammatory lipid-derived mediators, and neutrophil extracellular traps (NETs) to kill pathogens and limit inflammatory diffusion.<sup>[21]</sup> This robust host defense response also damages the surrounding tissue. Activation of the platelet and complementary system aggravated by tumor necrosis factor (TNF)-mediated expression of tissue factors (TFs) leads to microvascular thrombus formation, together with dysfunction of tight junctions and ion channels (e.g., epithelial sodium channels [ENaC] and sodium-potassium pump [Na<sup>+</sup>/K<sup>+</sup>-ATPase]), cell necrosis and apoptosis, hyaline membrane formation, and mechanical stretch. All of these further contribute to endothelial–epithelial barrier dysfunction, resulting in protein-rich fluid exudation from the capillary into interstitium and then the alveoli<sup>[22–25]</sup> ([Figure 1B](#)).

### Proliferative phase

In the proliferative phase, alveolar resident macrophages shift to the anti-inflammatory phenotype (i.e., M2), clearing neutrophils and excessive NETs through the efferocytosis process.<sup>[26,27]</sup> Alveolar epithelial cells (AECs) II begin to differentiate into AEC I, and tight junctions, along with adhere junctions, begin reconstructing and reestablishing the integrity of the endothelial–epithelial barrier.<sup>[28]</sup> The protein-rich edema fluid and hyaline membrane begin to be reabsorbed by re-expression of ion channels and aquaporins (AQPs).<sup>[29]</sup> However, prolonged lifespan and delayed apoptosis of neutrophils exaggerate NETs release that, along with decreased phagocytosis function of macrophages to apoptotic neutrophils and NETs, sustain inflammation in ARDS<sup>[30,31]</sup> ([Figure 2A](#)).

### Fibrosis phase

During the fibrosis phase, M2-like macrophages and activated AEC II release factors, including transforming growth factor (TGF)- $\beta$ , platelet-derived growth factor, and insulin-like growth factor-1 (IGF-1), induce extensive deposition of extracellular matrix. However, extensive basement membrane damage and lack of surfactant production can cause atelecta-



**Figure 1.** GC mechanisms in the exudative phase of ARDS. A: Direct and indirect insults damage the alveolar structure and microvasculature. B: During the exudative phase, alveolar resident macrophages are activated into M1-like macrophages, leading to the production of chemokines and proinflammatory cytokines that promote the accumulation of neutrophils and monocytes in the alveolus. To minimize the damage, activated neutrophils produce proinflammatory mediators such as ROS, NETs, COX-2, iNOS, MPO, and elastase. M1-like macrophages help T cells differentiate into T<sub>H</sub>1, T<sub>H</sub>2, T<sub>reg</sub>, and T<sub>H</sub>17 subgroups. AEC I and AEC II are injured, and surfactant production decreases. Platelet aggregation and microthrombus formation cause intra-microvascular and intra-alveolar thrombosis, all of which injure barrier functions, leading to intra-alveolar and interstitial edema and respiratory failure. GCs suppress the NF-κB pathway to inhibit downstream proinflammatory mediator release, enhance antigen uptake in DCs and NKCs, and contribute to anti-inflammation effects by elevating proportions of T<sub>H</sub>2, T<sub>reg</sub>, and T<sub>H</sub>17 subgroups, and reducing the T<sub>H</sub>1 subgroup. Despite repressing the expression of adhesion molecules to prevent adhesion and extravasation of neutrophils, GCs also induce expression and secretion of Anx-1 to further induce apoptosis of neutrophils in the inflammatory site. Created by Biorender.

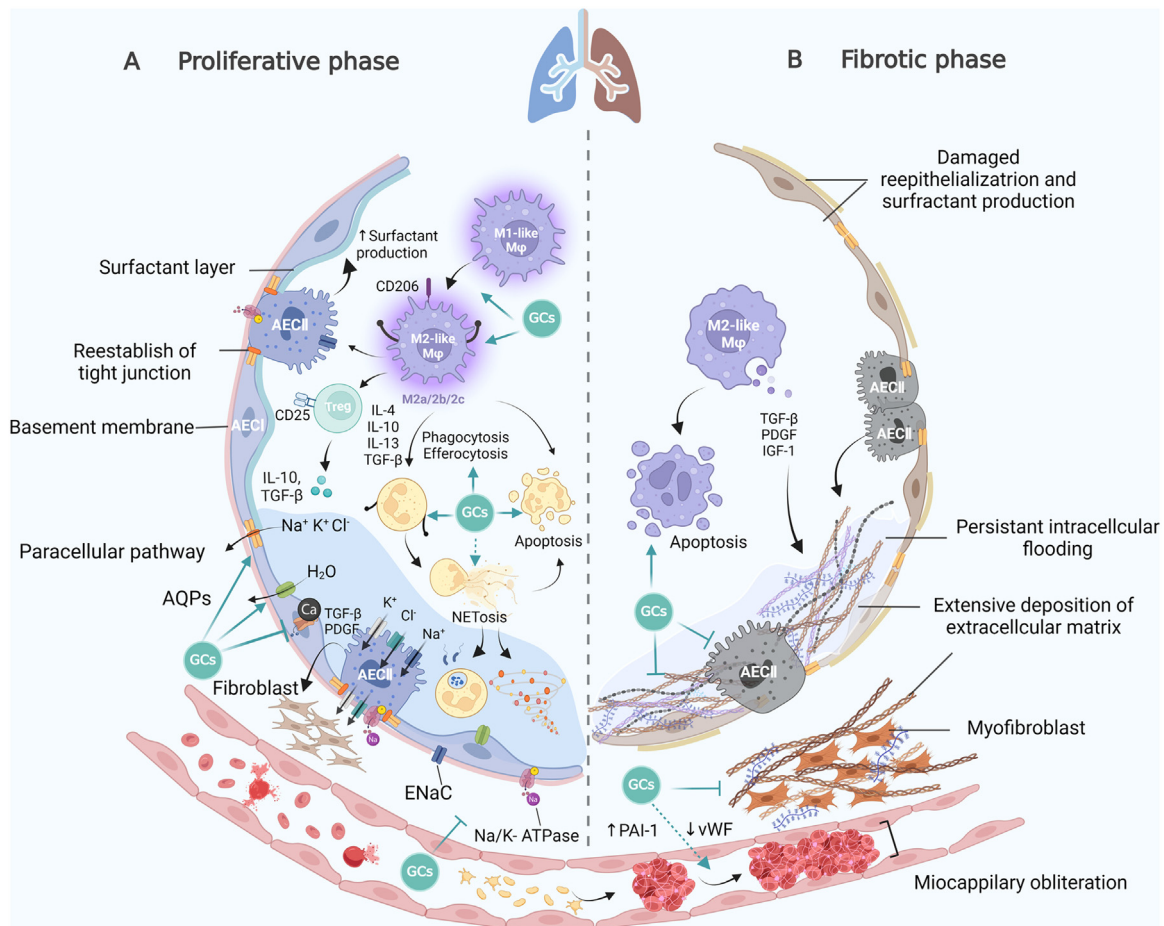
AEC: Alveolar epithelial cell; Anx-1: Annexin-1; AQP: Aquaporins; ARDS: Acute respiratory distress syndrome; COX-2: Cyclooxygenase-2; CXCL: C-X-C motif chemokine ligand; DAMP: Damage-associated molecular pattern; DCs: Dendritic cells; ENaC: Epithelial sodium channels; E-sel: E-selectin; GC: Glucocorticoid; IL: Interleukin; iNOS: Inducible nitric oxide synthase; l-sel: l-selectin; LTB4: Leukotriene B4; MHC: Major histocompatibility complex; MMPs: Matrix metalloproteinases; MPO: Myeloperoxidase; NETs: Neutrophil extracellular traps; NF-κB: Nuclear factor kappa-B; NKC: Natural killer cell; PAMP: Pathogen-associated molecular patterns; ROS: Reactive oxygen species; TCR: T cell receptor; T<sub>H</sub> cell: T helper cell; TNF: Tumor necrosis factor.

sis and persistent interstitial and intra-alveolar inflammatory exudation<sup>[18,32]</sup> (Figure 2B).

### Mechanisms of GCs in ARDS

GCs are considered a promising treatment of ARDS based on their anti-inflammatory, anti-oxidant, anti-fibrosis, and immunoregulation effects. However, the clinical effects remain controversial due to different ARDS phenotypes and variance in illness severity. Other influencing factors include GC type, initial time, dosage, and duration.<sup>[33]</sup> (The known mechanisms of GC actions are shown in Supplementary Box 1.)

Nuclear factor kappa-B (NF-κB) and activator protein-1, among other proinflammatory TFs, are primarily targeted by glucocorticoid receptor (GR)-mediated gene suppression to limit the inflammatory response.<sup>[34]</sup> Glucocorticoid-induced leucine zipper (GILZ), a key regulator of GC effects, downregulates toll-like receptor-2 (TLR-2) expression and NF-κB, activator protein-1, and mitogen-activated protein kinase pathway activities, thus inhibiting downstream proinflammatory gene expressions.<sup>[35,36]</sup> GCs can inhibit the NF-κB signal pathway by inducing inhibitor kappa B-α expression.<sup>[19]</sup> They can also upregulate mitogen-activated protein kinase phosphatase-1 expression, then attenuate extracellular signal-regulated kinase, p38



**Figure 2.** GC mechanisms in the proliferative and fibrotic phase of ARDS. A: The proliferative phase aims to resolve inflammation and reconstruct damaged structures. GCs induce phenotypic changes in macrophages from proinflammatory M1 to anti-inflammatory M2, activate macrophages to remove apoptotic cells, and improve the proportion of  $T_{reg}$  cells, which release  $TGF-\beta$ , contributing to inflammation resolution. GCs can augment NETs production for inflammation clearance, but excessive NETs production leads to persistent inflammation and aggressive injuries. Following GC therapy, ion channel (ENaC,  $Na^+/K^+$ -ATPase,  $Ca^{2+}/Cl^-/K^+$  pump, and AQPs) activity and quantity increase to hasten edema clearance. Surfactant production is increased with enhanced proliferation of AEC II. B: During the fibrotic phase, despite promoting re-epithelialization, GCs prevent the collagen deposition process and help to maintain the coagulation–fibrinolysis balance. Created by Biorender.

AEC: Alveolar epithelial cell; AQP: Aquaporin; ARDS: Acute respiratory distress syndrome; ENaC: Epithelial sodium channels; GC: Glucocorticoid; IGF: Insulin-like growth factor; IL: Interleukin; NETs: Neutrophil extracellular traps; PAI: Plasminogen activator inhibitor; PDGF: Platelet derived growth factor; TGF: Transforming growth factor; vWF: von Willebrand factor.

mitogen-activated protein kinase, and Jun N-terminal kinase signaling by either directly by binding to mitogen-activated protein kinase phosphatase-1 promoter or indirectly upregulating GILZ.<sup>[37,38]</sup> Annexin-1 (Anx-1), the first GC-induced annexin superfamily member to be characterized, inhibits the expression or activity of proinflammatory eicosanoids, cyclooxygenase (COX), and inducible nitric oxide (NO) synthase (iNOS) by repression of phospholipase A2.<sup>[39,40]</sup> Anx-1 can also prevent neutrophil adhesion to endothelial layers, and interfere with excessive inflammatory cell transmigration.<sup>[41]</sup> GCs can further induce vasorelaxation by activating phosphoinositide 3-kinase (PI3K) in a concentration-dependent manner, with lower dosages of GCs causing an increase in NO production and higher doses of GCs causing a decrease in NO production.<sup>[42]</sup> Moreover, GCs can block several inflammatory pathways by promoting expressions of specific proteins. Increased IL-10 expression inhibits  $NF-\kappa B$ , activates PI3K, downregulates TLR-4, and induces macrophage apoptosis, all of which help to resolve

inflammation.<sup>[43]</sup> In macrophages and endothelial cells, GCs protect endothelial barrier function by upregulating the sphingosine kinase 1 gene, which leads to elevated plasma sphingosine 1-phosphate.<sup>[44]</sup> Moreover, GCs stimulate the expression of cluster of differentiation 163 (CD163), a scavenger receptor that marks alternatively activated macrophages and monocytes, prompting them to phagocytose apoptotic cells and attenuate inflammation.<sup>[45]</sup> GCs also reduce blood flow to inflammatory areas by several mechanisms, consisting of upregulating endothelin and angiotensin-converting enzyme expression, sensitizing endothelial cells to vasoconstrictors, and suppressing the generation of vasodilators.<sup>[46]</sup>

Nearly all nucleated cells express GR, but GCs exert different actions on different cell types. The antigen uptake of dendritic cells (DCs) can be enhanced by GCs, which further downregulate the expression of major histocompatibility complex-II molecules, co-stimulatory molecules, and proinflammatory cytokines (e.g., IL-1, IL-6, and IL-12).<sup>[47]</sup> GCs can extend the lifes-



pan of natural killer cells (NKCs) stimulated by IL-2 and IL-12, protect NKCs from cytokine-induced death, and increase expression of interferon (IFN)- $\gamma$  and IL-6, which further exert anti-inflammatory effects.<sup>[48]</sup> GCs can suppress T cell expression of co-stimulatory molecules (CD2/CD8), cytokines (IL-1/IL-2/IL-5/IL-8/IL-13, IFN- $\alpha$ /IFN- $\beta$ /IFN- $\gamma$ ), and chemokines, resulting in potent T cell suppression.<sup>[49,50]</sup> Simultaneously, by inhibiting macrophages and DCs from producing IL-12 and IFN- $\gamma$ , GCs can reduce T<sub>h</sub>1 cell activation and promote T<sub>h</sub>17 cell differentiation, leading to increased expression of the anti-inflammatory mediator TGF- $\beta$  and introducing a shift from T<sub>h</sub>1 to T<sub>h</sub>2 immunity.<sup>[51–53]</sup> By boosting the number of T<sub>reg</sub> cells and enhancing their capacity to generate IL-10, T<sub>reg</sub> cells become resistant to GC-induced apoptosis.<sup>[54,55]</sup>

Innate immune cells, primarily neutrophils and macrophages, play an essential role during the inflammatory response. GCs stimulate the expression of TLR-2 and Nod-like receptor-3, increase circulating bone marrow-derived neutrophils, and enhance the innate immune system's ability to react instantly to inflammation.<sup>[56,57]</sup> Tissue infiltration of neutrophils can be targeted by GCs via (1) down-regulated expressions of L, P, and E-selection to reduce capture and rolling<sup>[58]</sup> and (2) reduce the adhesion molecules on both the endothelium<sup>[59]</sup> and leukocytes<sup>[60]</sup> to prevent adhesion and detachment. GCs also reduce expressions of ROS, COX-2, and iNOS<sup>[61,62]</sup> and inhibit chemotaxis and phagocytosis of neutrophils.<sup>[63]</sup> GCs inhibit the synthesis of proinflammatory mediators by enhancing IL-1 receptor-associated kinase-M expression in both macrophages and epithelial cells.<sup>[64,65]</sup> Furthermore, GCs can promote an anti-inflammatory phenotype in monocytes by preventing oxidative stress-induced apoptosis, permitting them to migrate rapidly into inflammatory sites.<sup>[66]</sup>

A hallmark of ARDS, the inflammatory pulmonary edema caused by the damaged endothelial–epithelial barrier is also the key target of exogenous GCs. Inflammatory cytokines can prevent fluid transport by inactivation of ENaC and Na<sup>+</sup>/K<sup>+</sup>-ATPase.<sup>[29]</sup> GCs can activate the PI3K/phosphatidylinositol-3,4,5-trisphosphate (PIP3) pathway or increase SGK1 synthesis to inhibit iNOS, then activate ion channels.<sup>[24]</sup> GCs control Na<sup>+</sup> transport by inducing steroid-induced proteins that alter ENaC trafficking, assembly, and degradation.<sup>[24]</sup> GCs also down-regulate channel permeability by inhibiting AQP.<sup>[67]</sup> It has also been suggested that GCs rapidly decrease basal intracellular Ca<sup>2+</sup> levels by interfering with Ca<sup>2+</sup> cycling from intracellular stores into the cytoplasm, reducing ATP consumption and ROS production, thus affecting cellular energy metabolism.<sup>[68]</sup>

During the rehabilitation and fibrotic phase of ARDS, GCs prevent collagen deposition and re-epithelialization, to restore tissue integrity and function.<sup>[69,70]</sup> After administering GCs, levels of plasminogen activator inhibitor (PAI)-1 increase, while von Willebrand factor and fibrinogen levels decline, potentially maintaining the proper coagulation–fibrinolysis balance.<sup>[71]</sup> Moreover, GILZ acts as a negative regulator of Ras- and Raf-induced proliferation and a critical mediator of GCs antiproliferative activity.<sup>[72]</sup>

## Heterogeneity of ARDS

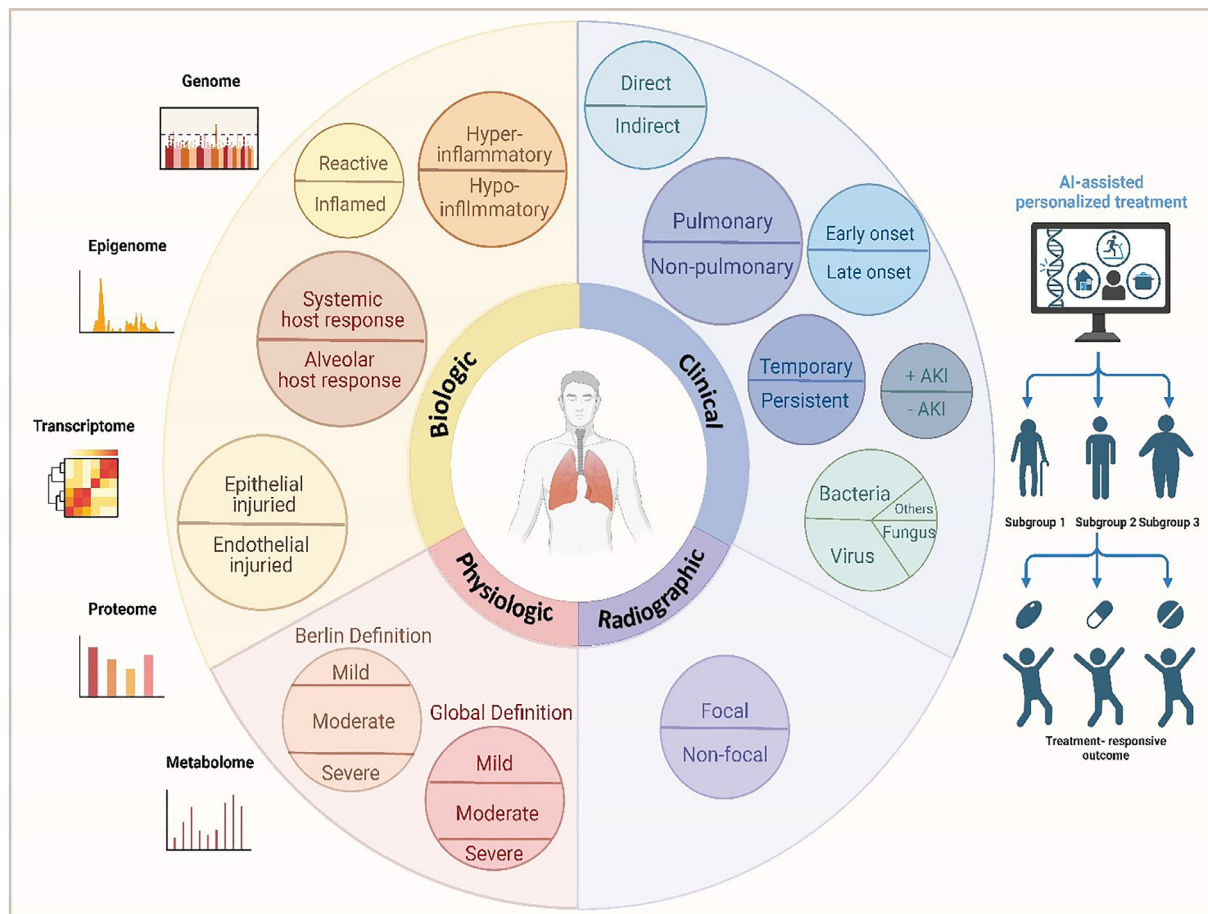
A main reason why observational and randomized trials fail is that ARDS is, by nature, heterogeneous.<sup>[73]</sup> Negative re-

sults may indicate a treatment that is truly ineffective or a masking signal from harm in a subset of patients with a similar phenotype.<sup>[74]</sup> Identifying a patient's ARDS endotype and subphenotype facilitates assigning them to various treatment groups and assessing results more precisely. Both prognostic enrichment (identifying subgroups who are more likely to have a particular endpoint) and predictive enrichment (identifying subgroups who are more likely to respond to a given intervention due to the mechanism of benefit) help to improve clinical trial efficacy.<sup>[75,76]</sup> See [Figure 3](#) for a schematic representation of ARDS heterogeneity.

Many factors—including physiological, clinical, radiological, and biological—are considered to identify ARDS subphenotypes. Several physiological parameters can be considered to categorize patients with ARDS, including PaO<sub>2</sub>/FiO<sub>2</sub>, dead space fraction, driving pressure, and ventilatory ratio. There is a positive correlation between illness severity and mortality, according to both the Berlin and global definitions, both of which use PaO<sub>2</sub>/FiO<sub>2</sub> as the illness severity criterion.<sup>[4,77]</sup> One notable drawback of PaO<sub>2</sub>/FiO<sub>2</sub> is its significant dependence on ventilator settings, particularly positive end-expiratory pressure, which may swiftly transfer one subset of patients to another.<sup>[78,79]</sup> In a recent study, investigators also distinguished recruitable and non-recruitable phenotypes using CT imaging, respiratory mechanics, and gas exchange.<sup>[80]</sup> These phenotypes are distinguished by their notably different reactions to standardized recruitment protocols.<sup>[80]</sup> The efficacy of using other physiological parameters (e.g., airway driving pressure and transpulmonary pressure) to guide intervention classification has yet to be fully elucidated.<sup>[81–83]</sup>

Clinical phenotypes (including pneumonia/non-pulmonary sepsis/trauma, direct/indirect, bacteria/virus/fungal/other, early/late stage, temporary/persistent, and acute kidney injury) act as an important framework for ARDS management and prognosis<sup>[79,84]</sup>; this indicates differences in incidence, risk strategy, and mortality in patients under different ARDS pathogenesis types. The main drawback of clinical phenotypes is that they make it difficult to classify patients because they have unique physiologies and respond differently to treatments. While ARDS is a clinical diagnosis, clinical characteristics may not be precise enough to differentiate among patients' biological heterogeneity for matching targeted therapies to the most active, relevant pathways.<sup>[73]</sup>

Radiographic heterogeneity was reported in a study in which lung morphology was classified into focal and non-focal phenotypes.<sup>[85]</sup> The Lung Imaging for Ventilator Setting trial found no difference in 90-day mortality between standard and personalized ventilation strategies for focal or non-focal moderate-to-severe ARDS, but it did find a 21% misclassification at randomization.<sup>[86]</sup> Mortality was significantly higher among patients whose ventilator strategy was misaligned, and excluding the misaligned group from the whole patient group has a potential survival benefit. Effectively identifying and allocating patients to the correct phenotype are crucial for future clinical trials and precision medicine. Since plain chest radiographs are more readily available than CT, radiographic assessment of lung edema scoring can be used to quantify both the extent and density of alveolar edema; previous studies have found that radiographic assessment of lung edema score changes over time are associated with ARDS clinical outcome.<sup>[87,88]</sup>



**Figure 3.** ARDS heterogeneity and future perspectives. The ARDS is heterogeneous by nature and markedly impacts treatment efficacy. The center of the donut graph represents four main ARDS heterogeneity factors: clinical, physiological, radiographical, and biological. Circles within each section show identified subphenotypes. Omics approaches (left) and AI-assisted conceptual models (right) may help to identify specific subphenotypes and promote precision medicine. Created by Biorender. AI: Artificial intelligence; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome.

With their lower chance of misclassification, biological markers are considered the most trustworthy for subphenotyping patients with ARDS. Several plasma biomarkers have been tested, including markers of inflammatory, endothelial injury, and coagulation disorder, all of which had prognostic value.<sup>[89,90]</sup> In addition, “hyperinflammatory” and “hypoinflammatory” subphenotypes were identified by the latent class analysis,<sup>[91]</sup> while “reactive” and “uninflamed” subphenotypes were identified using hierarchical clustering and canonical pathway analysis.<sup>[92,93]</sup> Three-variable (IL-8, bicarbonate, and protein C) and four-variable (addition of vasopressor) parsimonious models have been developed to improve efficacy,<sup>[94,95]</sup> though prospective validation will be needed.<sup>[96]</sup> Airspace sampling, such as bronchoalveolar lavage fluid<sup>[96]</sup> and heat moisture exchange filter fluid,<sup>[97]</sup> could also provide evidence of lung injury that plasma cannot, deepening our understanding of ARDS mechanisms. Omics technologies such as genomic, transcriptomic, proteomic, and metabolomic offer promising opportunities for pathway-specific interventions<sup>[96,98–101]</sup>; however, these approaches are still in early development and not yet ready for patient use.<sup>[102]</sup>

Since ARDS develops rapidly, intervention should occur at clinical symptoms onset. Preventing unsafe exposure to immunomodulating drugs, like GCs, is critical,<sup>[103]</sup> highlight-

ing that reliable identification of patient phenotype is a major hurdle for precision medicine clinical trials in critically ill populations.<sup>[104]</sup> Point-of-care clinical biomarker assays are needed to enable appropriate pre-intervention phenotyping.<sup>[105]</sup> ARDS heterogeneity includes severity, stage, etiology, clinical trial design, and population, all of which may be useful for distinguishing phenotypes for specific “treatable traits” beyond the current ARDS definition.<sup>[106–108]</sup> To better understand the important nodes of underlying physiological mechanisms, novel interventions of each subphenotype must be tested through pre-clinical research, translational clinical cohort studies, and randomized trials.<sup>[73]</sup> Well-designed clinical trials should also be designed to increase participant representativeness, including those from both resource-rich and resource-poor settings, to decrease trial population heterogeneity.<sup>[74]</sup>

### GC Therapy in Non-COVID-19-Related ARDS

As GCs have been considered both standard and exploratory treatments for preventing the spread of inflammation and improving survival, previous studies have tested different regimens in terms of timing, dose, course, and withdrawal, thus laying the groundwork for GC therapy in ARDS.<sup>[109,110]</sup> A comparison of GCs is presented in Supplementary Box 2. Representative ran-

domized controlled trials (RCTs) for ARDS and severe pneumonia are summarized in Table 2.

### Who benefits from GCs therapy?

#### Intervention stage

The first step is to identify patients who will benefit from GCs. The effects of a low-dose prolonged methylprednisolone regimen for severe early ARDS ( $\leq 72$  h of symptom onset) were examined in a 2007 multicenter RCT ( $n=91$ ), reported by Meduri et al.<sup>[111]</sup> Those receiving methylprednisolone had significantly: mitigated systemic inflammation, accompanied by lower C-reactive protein levels; improved pulmonary and extrapulmonary organ dysfunction, evidenced by lower lung injury and multiple organ dysfunction syndrome scores; and shortened mechanical ventilation (MV) duration and ICU length of stay (LOS). Unfortunately, studies have failed to demonstrate GC efficacy in late-stage ARDS. Although data from the ARDS Network demonstrated that GCs improved pulmonary function from 7 days to 14 days after ARDS diagnosis, the therapeutic effect did not persist when GCs were delivered after that window, based on significantly higher 60-day and 180-day mortality rates in subgroup analyses.<sup>[112]</sup> Early GC treatment in patients with severe community-acquired pneumonia prevented progression to septic shock (0% vs. 43%) and ARDS (0% vs. 17%),<sup>[113]</sup> while prolonged methylprednisolone treatment in early ARDS prevented progression to unresolving ARDS (8% vs. 36%).<sup>[111]</sup> A meta-analysis of 8 RCTs and 10 cohort studies reported that patients with persistent ARDS appeared to benefit more if GCs were given within 14 days after symptom onset, further confirming the ARDS Network findings.<sup>[114]</sup>

#### Bacterial, viral, fungal, and other pathogenic infections

Notably, the effects of early initial GC administration did not persist in patients with influenza-induced ARDS. A retrospective analysis of the Recherche en Ventilation Artificielle-SRLF (REVA-SRLF) trial conducted during the A/H1N1 pandemic found that early initiation (within  $\leq 3$  days of initial MV) with moderate-dose GCs was associated with increased mortality.<sup>[115]</sup> Moreover, GC therapy was associated with an increased risk of myocardial and liver injury, shock, MV duration, and delayed viral airway clearance, consistent with studies in severe acute respiratory syndrome-associated coronavirus (i.e., severe acute respiratory syndrome coronavirus 2 and Middle East respiratory syndrome coronavirus).<sup>[116,117]</sup> Thus, routine GCs in patients with virus-induced ARDS should be used with caution, as it may be detrimental to multi-organ function.

#### Preventive and rescue administration

Preventive GC administration has not been shown to prevent either the development of, or reverse, ARDS in patients with sepsis.<sup>[118]</sup> A meta-analysis of four studies assessing preventive GC treatment found a trend toward it increased odds of patients who developed ARDS, and increased mortality risk in those who subsequently developed ARDS.<sup>[119]</sup>

### Can mortality be reduced after GC treatment?

Due to inconsistent study results, it remains uncertain whether GCs reduce mortality among patients with ARDS. Hydrocortisone administration improved pulmonary function but

did not reduce 28-day mortality (hazard ratio [HR]=0.80, 95% confidence interval [CI]: 0.46 to 1.41) in early sepsis-associated ARDS ( $n=197$ ).<sup>[120]</sup> A systemic review of 48 RCTs found that although GCs improved ventilator-free days (VFD) up to day 28 (mean difference=4.09, 95% CI: 1.74 to 6.44, low-certainty evidence) and might lower early all-cause mortality (risk ratio [RR]=0.77, 95% CI: 0.57 to 1.05; low-certainty evidence), they did not reduce late all-cause mortality (relative risk=0.99, 95% CI: 0.64 to 1.52; very low-certainty evidence).<sup>[121]</sup> The task force for the Critical Illness-Related Corticosteroid Insufficiency (CIRCI) guideline found that prolonged GC therapy was associated with increased VFD and ICU-free days and higher survival,<sup>[122]</sup> indicating that their therapeutic benefits outweighed potential risks. The DEX-ARDS RCT ( $n=277$ ), conducted after publication of the CIRCI guidelines, found that early administration of dexamethasone (DEX) for 10 days resulted in reduced MV duration (between-group difference 4.8 days; 95% CI: 2.57 to 7.03) and all-cause mortality on day 60 (between-group difference 15.3%; 95% CI: -25.9 to 4.9%).<sup>[123]</sup>

### How to determine an optimal therapeutic regimen?

#### GC therapy dose

Attention needs to be paid to GC dosage and use duration. From the mid-1950s to the 1980s, high-dose GCs were used to treat ARDS, with few survival benefits observed, especially from a short course of high-dose GCs. An observational study in which 105 patients with ARDS were allocated to high-dose or low-dose GCs (mean doses are 175 mg/day and 88.5 mg/day, respectively) according to their condition showed that except for a markedly decreased IL-18 and significant improvement in oxygenation among survivors, high-dose GC was related to higher 45-day mortality.<sup>[124]</sup> Kaplan–Meier analysis revealed that when the GC dosage was equal to 146.5 mg/day of methylprednisolone, it had the highest sensitivity and specificity for predicting death, indicating that high-dose GC was an independent risk factor for death. Collectively, high-dose GC therapy is not recommended for patients with either ARDS or sepsis according to current evidence.<sup>[125]</sup> In addition, a series of studies of patients with sepsis or septic shock showed no survival benefit, and potential harm in patients with normal ( $>9$  g/dL) plasma cortisol.<sup>[126,127]</sup> Since the 1990s, physiologic steroid therapy (also known as a “supraphysiologic” or “stress” dose) in patients with ARDS and sepsis has been encouraging, including improved respiratory function, decreased lung and systemic inflammation, and survival benefits.<sup>[128,129]</sup> Most studies have used a protocol of  $\leq 2$  mg/(kg·day) with a gradual taper, but a more precise recommendation was made considering ARDS timing: methylprednisolone  $\leq 1$  mg/(kg·day) for early ARDS ( $\leq 72$  h of onset) and 2 mg/(kg·day) for persistent/unresolving ARDS ( $\geq 5$  days of onset), combined with a slow dosage reduction (9–12 days).<sup>[130]</sup> Although a null effect for low-dose steroid-based mortality efficacy in severe sepsis and septic shock could not be excluded, there appeared to be credible evidence for shock reversal efficacy; similarly, the beneficial effects of low-dose steroids were highly dependent on patient age and underlying risk factors.<sup>[131]</sup>

#### GC therapy duration

Previous clinical and experimental studies have demonstrated that GC exposure duration is critical to regulating cy-

**Table 2**  
RCTs of ARDS.

Trial/author (year)	Design	Period	Participants	No. of patients (GCs/control)	Interventions	Duration (days)	Primary outcome (GCs vs. control)	Secondary outcomes	Others
Burnard et al. <sup>[176]</sup> (1987)	Country: USA Multicenter (7 ICUs) Placebo-controlled Two parallel groups	June 1983–November 1985	ARDS	99 (50/49)	Methylprednisolone (bolus of 30 mg/kg for every 6 h for four doses)	1	No difference in mortality rate during 45-day follow-up (60% vs. 63%, $P=0.74$ )	Lower reversal of chest radiograph and arterial blood gases were observed (9% vs. 56%, $P < 0.018$ )	NA
Meduri et al. <sup>[127]</sup> (1998)	Country: Memphis Multicenter (4 ICUs) Placebo-controlled Two parallel groups	October 1994–November 1996	Severe persistent ARDS	24 (16/8)	Methylprednisolone (bolus of 2 mg/kg followed by every 6 h: 2 mg/(kg·day) for 14 days, 1 mg/(kg·day) for 7 days, 0.5 mg/(kg·day) for 7 days, 0.25 mg/(kg·day) for 2 days, and 0.025 mg/(kg·day) for 2 days)	14	On day 10: Reduced LIS (1.7 vs. 3.0, $P < 0.001$ ) Improved PaO <sub>2</sub> : FiO <sub>2</sub> (262 vs. 148, $P < 0.001$ ) ICU mortality: 0/16 (0%) vs. 5/8 (62%) ( $P=0.002$ ) Hospital mortality: 2/16 (12%) vs. 5/8 (62%) ( $P=0.03$ )	Decreased MODS score (0.7 vs. 1.8, $P < 0.001$ ) No increased rate of infections	Four patients in the control group crossed over because of failure to improve outcomes
Confalonieri et al. <sup>[113]</sup> (2005)	Country: Italy Multicenter (6 ICUs) Placebo-controlled Two parallel groups	July 2000–March 2003	Severe CAP	48 (24/24)	Hydrocortisone (bolus of 200 mg followed by infusion of 240 mg/day at a rate of 10 mg/h)	7	On day 8: Improved PaO <sub>2</sub> : FiO <sub>2</sub> $\geq 300$ mmHg (16/23 vs. 5/23, $P=0.0002$ ) Reduced MODS score (0.3±0.5 vs. 1.0±0.9, $P=0.003$ )	GCs treatment was associated with decreased CRP levels (18 mg/dL vs. 34 mg/dL, $P=0.01$ ), delayed septic shock (0% vs. 13%, $P=0.001$ ), reduced in-hospital stay and mortality (all $P < 0.01$ ) on day 8	NA
ARDS Network/Steinberg et al. <sup>[112]</sup> (2006)	Country: USA Multicenter (25 ICUs) Placebo-controlled Two parallel groups	August 1997–November 2003	Persistent ARDS	180 (89/91)	Methylprednisolone (bolus of 2 mg/kg, followed by 0.5 mg/(kg·6 h) for 14 days, 0.5 mg/(kg·12 h) for 7 days, and tapered over 2–4 days)	23–25	No difference in 60-day mortality between groups (29.2% vs. 28.6%, $P=1.0$ )	Improvement in MV-free days ( $P < 0.001$ ), ICU-free days ( $P=0.02$ ), and organ failure-free days ( $P < 0.001$ ) at day 28 Higher rate of neuromuscular weakness (9 vs. 0, $P=0.001$ )	Significantly increased rate of 60-day and 180-day mortality when GCs administered $\geq 14$ days before the onset of ARDS More likely to be re-intubated after GCs treated (28% vs. 9%, $P=0.006$ )
Anname et al. <sup>[177]</sup> (2006)	Country: France Multicenter (19 ICUs) Placebo-controlled <i>Post hoc</i> analysis Two parallel groups	October 1995–February 1999	Septic shock-associated early ARDS	177 (85/92)	Hydrocortisone (50 mg/6 h) together with fludrocortisone (50 $\mu$ g orally daily)	7	Decreased 28-day survival in non-responders (53% vs. 75%, HR=0.57, 95% CI: 0.36 to 0.89, $P=0.013$ )	ICU mortality in non-responders (RR=0.73, 95% CI: 0.57 to 0.94, $P=0.01$ ) Hospital mortality in non-responders (RR=0.75, 95% CI: 0.59 to 0.96, $P=0.016$ ) No significant difference in adverse events (all $P > 0.05$ )	Not all patients received lung-protective ventilation (mean tidal volume in all patients with ARDS >8 mL/kg)
Meduri et al. <sup>[111]</sup> (2007)	Country: USA Multicenter (5 ICUs) Placebo-controlled Two parallel groups	April 1997–April 2002	Severe early ARDS ( $\leq 72$ h)	91 (63/28)	Methylprednisolone (bolus of 1 mg/kg followed by 1 mg/(kg·day) continuous infusion for 14 days, 0.5 mg/(kg·day) for 7 days, 0.25 mg/(kg·day) for 4 days, and 0.125 mg/(kg·day) for 3 days)	28	On day 7: 2-fold reduction of a 1-point reduction in LIS (69.8% vs. 35.7%, $P=0.002$ ) and MODS scores (0.90±1.1 vs. 1.9±1.4; $P=0.002$ ) More patients breathing without assistance (54% vs. 25%; $P=0.01$ )	Shorter length of ICU stay (7 days vs. 14.5 days; $P=0.007$ ) Lower rate of ICU mortality (20.6% vs. 42.9%; $P=0.03$ ) Fewer new infections (42.9% vs. 60.7%; $P=0.002$ )	More received open-label methylprednisolone (7.9% vs. 35.7%; $P=0.002$ )

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Table 2 (continued)

Trial/author (year)	Design	Period	Participants	No. of patients (GCs/control)	Interventions	Duration (days)	Primary outcome (GCs vs. control)	Secondary outcomes	Others
Meijvis et al. <sup>[178]</sup> (2011)	Country: Netherlands Multicenter (2 ICUs) Placebo-controlled	November 2007–September 2010	Severe CAP	304 (151/153)	DEX (5 mg daily)	4	Reduced length of hospital stay (6.5 days vs. 7.5 days, 95% CI: 0 to 2 days, $P=0.048$ )	No difference in hospital mortality and 30-day mortality (all $P > 0.05$ ) Higher rate of hyperglycemia (67/151 [44%] vs. 35/153 [23%], $P < 0.0001$ )	NA
Tongyoo et al. <sup>[120]</sup> (2016)	Country: Thailand Single-center Placebo-controlled Two parallel groups	December 2010–December 2014	Sepsis-associated ARDS	197 (98/99)	Hydrocortisone (200 mg/day in 4 bolus of 50 mg)	7	No difference in mortality at day 28 (22.5% vs. 27.3%, RR=0.82, 95% CI: 0.50 to 1.34, $P=0.51$ )	Similar time to remove vital organ support (HR=0.74, 95% CI: 0.51 to 1.07, $P=0.107$ )	Improvement in the PaO <sub>2</sub> : FiO <sub>2</sub> ( $P=0.001$ ) and LIS ( $P=0.01$ ) Higher rate of hyperglycemia (80.6% vs. 67.7%, $P=0.04$ )
DEXA-ARDS/Villar et al. <sup>[123]</sup> (2020)	Country: Spain Multicenter (17 ICUs) Placebo-controlled Two parallel groups	March 2013–December 2018	Moderate-to-severe ARDS	277 (139/138)	DEX (20 mg/day bolus for 5 days followed by 10 mg/day for 5 days)	10	Longer MV-free days on day-28 (MD=4.8 days, 95% CI: 2.57 to 7.04, $P < 0.0001$ )	Lower all-cause mortality on day-60 (between-group difference -15.3%, 95% CI: -25.9 to -4.9, $P=0.0047$ )	Higher re-intubation rate with DEX compared with control (12 [8.6%] vs. 7 [5.1%])
CoDEX trial/Angus et al. <sup>[179]</sup> (2020)	Country: Brazil Multicenter (41 ICUs) Placebo-controlled Two parallel groups	June 2020–July 2020	Moderate-to-severe ARDS	299 (151/148)	DEX (20 mg/day bolus for 5 days followed by 10 mg/day for 5 days or until discharge)	NA	Longer MV-free days on day-28 (MD=2.26 days, 95% CI: 0.2 to 4.38, $P=0.04$ )	No difference in all-cause mortality, ICU-free days, and MV-free days at day-28	NA
Grageb-Chatti et al. <sup>[155]</sup> (2021)	Country: France Multicenter (3 ICUs) Placebo-controlled Two parallel groups	March 10–29, 2020 and August 2020–November 2020	COVID-19-related ARDS requiring invasive MV	151 (84/67)	DEX (6 mg/day for 10 days)	10	DEX did not significantly increase the incidence of VAP or BSI	DEX treatment was associated with more VFD at day-28	NA
RECOVERY trial/Horby et al. <sup>[145]</sup> (2021)	Country: UK Multicenter (176 ICUs) Placebo-controlled Two parallel groups	March 2020–June 2020	COVID-19	6425 (2104/4321)	DEX (6 mg/day for 10 days)	10	Lower 28-day mortality among those who were receiving either invasive MV or oxygen alone at admission (aRR=0.83, 95% CI: 0.75 to 0.93, $P < 0.001$ )	NA	DEX treatment showed no benefit and even harm among patients who did not require oxygen
Moreno et al. <sup>[150]</sup> (2021)	Country: Spanish, Andorran, and Irish Multicenter (70 ICUs) Placebo-controlled Two parallel groups	February 2020–September 2020	COVID-19-related ARDS requiring invasive MV	1835 (1117/781)	Methylprednisolone was used in 76.6% and DEX was used in 22.1% of patients. Mean duration of methylprednisolone and DEX treatment was 5 days and 10 days, respectively	NA	ICU mortality did not differ between groups (33.8% vs. 30.9%, $P=0.28$ )	GCs treatment at ICU admission was associated with survival benefit (HR=0.53, 95% CI: 0.39 to 0.72) After the 17th day of admission, GCs treatment increased ICU mortality (long-term HR=1.68, 95% CI: 1.16 to 2.45)	Specific subgroups (age <60 years, severe ARDS) could benefit from GCs treatment
Martinez-Guerra et al. <sup>[159]</sup> (2022)	Country: Mexico Single-center Placebo-controlled Two parallel groups	March 2020–September 2020	Severe COVID-19-related ARDS	1540 (688/852)	DEX (6 mg/day for 10 days) after June 17, 2020	NA	Reduced in-hospital mortality (18% vs. 31%, $P < 0.01$ )	GCs treatment resulted in longer time before MV (5 days vs. 3 days, $P < 0.01$ ), and more HAP (20% vs. 10%, $P < 0.01$ )	NA
Lamouche-Wilquin et al. <sup>[154]</sup> (2022)	Country: France Multicenter (15 ICUs) Placebo-controlled Two parallel groups	February 2020–December 2020	COVID-19-related ARDS	670 (369 early GCs/301 no early GCs)	DEX was used in 91% (336/369) of the early admitted patients, while methylprednisolone was used in 36% (19/53) beyond 24 h of admission	NA	The incidence of VAP was higher with early GCs treatment (HR=1.29, 95% CI: 1.05 to 1.58, $P=0.016$ )	NA	VAP was associated with higher day-90 mortality, but early GCs treatment was not

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Table 2 (continued)

Trial/author (year)	Design	Period	Participants	No. of patients (GCs/control)	Interventions	Duration (days)	Primary outcome (GCs vs. control)	Secondary outcomes	Others
Reyes et al. <sup>[153]</sup> (2022)	Country: Latin, USA, and Europe Multicenter (84 ICUs) Placebo-controlled Two parallel groups	March 2020–January 2021	Severe COVID-19-related ARDS	3777 (2065/1712)	DEX dose and duration were determined by the attending physician	NA	Significant higher proportion of VAP was found (17.1% vs. 13.2%, $P=0.014$ )	NA	DEX treatment was considered an adjusted risk factor of ICU-acquired respiratory infections
Maskin et al. <sup>[180]</sup> (2022)	Country: Argentina Multicenter (4 ICUs) Dose-controlled Two parallel groups	June 2020–March 2021	COVID-19-related ARDS requiring invasive MV	98 (49 low-dose DEX/49 high-dose DEX)	DEX (6 mg/day for 10 days in low-dose group; 16 mg/day for 5 days followed by 8 mg/day for 5 days)	10	No difference in VFD ([0–14] day vs. [0–1] day, $P=0.231$ ) or mean duration of MV (19±18 days vs. 25±22 days, $P=0.078$ ) within 28 days after inclusion between groups	Higher cumulative hazard of successful discontinuation from MV in the high-dose group (HR=1.84, 95% CI: 1.31 to 2.5, $P < 0.001$ )	NA
Scaravilli et al. <sup>[181]</sup> (2022)	Country: Italy Multicenter (4 ICUs) Propensity-matched cohort study Two parallel groups	February 2020–December 2020	COVID-19-related ARDS requiring invasive MV	316 (158/158)	DEX (6 mg/day for 10 days)	10	Higher VAP incidence and risk for VAP	Mortality was similar between groups	VAP was associated with longer ICU and in-hospital LOS, and MV rate. VAP increased mortality (RR=1.64, 95% CI: 1.02 to 2.65, $P=0.04$ )
RECOVERY trial/RECOVERY Collaborative Group <sup>[148]</sup> (2023)	Country: UK, Asia, and Africa Multicenter (93 ICUs) Placebo-controlled Two parallel groups	May 2021–May 2022	COVID-19	1272 (659/613)	DEX (20 mg/day bolus for 5 days followed by 10 mg/day for 5 days or until discharge)	NA	Higher dose GCs result in higher day-28 mortality compared with usual care (123/659 [19%] vs. 75/613 [12%], RR=1.59, 95% CI: 1.12 to 2.10, $P=0.0012$ )	NA	Higher dose DEX treatment resulted in an increase in hyperglycemia requiring an increased insulin dose

ARDS: Acute respiratory distress syndrome; BSI: Blood stream infections; CAP: Community-associated pneumonia; CI: Confidence interval; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; DEX: Dexamethasone; FiO<sub>2</sub>: Fraction of inspired oxygen; GCs: Glucocorticoids; HAP: Hospital-acquired infections; HR: Hazard ratio; ICU: Intensive care unit; LIS: Lung injury scores; LOS: Length of stay; MD: Mean difference; MODS: Multiple organ dysfunction syndrome; MV: Mechanical ventilation; NA: Not available; PaO<sub>2</sub>: Partial pressure of oxygen in arterial blood; RCTs: Randomized controlled trials; RR: Risk ratio; VAP: Ventilator-associated pneumonia; VFD: Ventilator-free day.

tokine production and that premature discontinuation leads to clinical deterioration (i.e., increased inflammatory markers and worsening multiple organ dysfunction).<sup>[132,133]</sup> In the ARDS Network, patients in the methylprednisolone group were able to breathe on their own sooner, but one-quarter of them resumed MV after rapid steroid discontinuation (28% vs. 9%). This result was probably attributable to the negative effects of GCs, such as neuromyopathy and shock recrudescence.<sup>[112]</sup> The potent anti-inflammatory effects of GCs were achieved at the expense of reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, with the risk of treatment-associated adrenal insufficiency in patients who are critically ill.<sup>[134]</sup>

Extended GC exposure restores GR quantity and function, resulting in lower inflammatory marker levels and higher functional surfactant levels.<sup>[130]</sup> A recent ARDS Network reanalysis reinforced that abruptly discontinuing GCs causes inflammatory rebound, which may explain the increased return to MV and mortality,<sup>[135]</sup> and that gradual tapering is essential to maintain inflammation resolution, restore tissue homeostasis, and suppress the HPA axis to forestall disease relapse because of inflammation rebound.<sup>[111,130]</sup> Hence, resuming GC administration should be considered if the patient's condition rapidly deteriorates after it is abruptly discontinued. With ongoing uncertainties, an individualized dosage regimen is required according to the underlying disease, organ function, and initial GC timing and options, rather than ARDS *per se*.<sup>[136]</sup>

Benefits and risks, as well as costs, must be balanced in treatment decision-making. We propose a tailored approach in which steroids are administered regularly to those most likely to benefit from them, avoided in patients at higher harm risk, and carefully evaluated on a case-by-case basis in those with intermediate risks/benefits.

### GC Therapy in COVID-19-Related ARDS

COVID-19 has become the leading etiology of acute respiratory failure.<sup>[137,138]</sup> Severe acute respiratory syndrome coronavirus 2, the virus that causes COVID-19, attaches and internalizes along with the membrane-bound protein angiotensin converting enzyme (ACE-2) to cause intracellular damage.<sup>[139]</sup> Compared with non-COVID-19 ARDS, COVID-19-induced ARDS is characterized by reduced IL-6 expression,<sup>[140]</sup> lower total white cell count, and higher platelet count and fibrinogen.<sup>[141]</sup> DEX was reported to be therapeutic in severe COVID-19 by suppressing the IFN signal, expanding immunosuppressive immature neutrophils, and remodeling cellular interactions.<sup>[142]</sup> GCs also inhibit ROS generation in circulating T cells<sup>[143]</sup> and decrease CD4<sup>+</sup> counts and human leukocyte antigen expression in circulating monocytes.<sup>[144]</sup>

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial reported that DEX (6 mg/(kg·day) for 10 days) reduced 28-day mortality by one-third in patients undergoing invasive MV, and one-fifth in those who received oxygen supply, but did not benefit those who did not receive oxygen.<sup>[145]</sup> Several studies have demonstrated the positive effects of GCs on survival, without elevated risk of adverse events.<sup>[146,147]</sup> Although RECOVERY survival benefits results led to several recommendations regarding GC therapy in patients with severe COVID-19, controversial results remain. The latest RECOVERY trial ( $n=1272$ ) reported significantly increased mortality risk in

patients hospitalized with COVID-19 who require either no oxygen or simple oxygen with higher-dose GCs (DEX 20 mg/day for 5 days followed by 10 mg/day for 5 days or until discharge), compared with usual care which included low-dose GCs.<sup>[148]</sup> In the COVID-19 Dexamethasone (CoDEX) trial, in patients with moderate-to-severe COVID-19 ( $n=299$ ), DEX administration led to no significant improvements in ICU mortality, ICU LOS, or MV duration.<sup>[149]</sup> A large retrospective cohort study of patients with COVID-19 with MV also identified a time-dependent effect for survival benefit, with a protective effect when GCs were administered within 2 weeks of diagnosis.<sup>[150]</sup> Recently, high-dose GCs (1 mg/kg methylprednisolone) treatment in patients with COVID-19 and non-resolving ARDS who had been treated with DEX as standard of care had higher 90-day mortality (adjusted HR=1.65, 95 % CI: 1.03–2.63).<sup>[151]</sup> The One Year Follow-ups of Patients Admitted to Spanish Intensive Care Units Due to COVID-19 (CIBERESUCICOVID) trial found a protective effect on 90-day mortality, even in specific subgroups (i.e., age  $\geq 60$  years, higher baseline severity, those who required MV at ICU admission).<sup>[152]</sup> A large, multicenter RCT ( $n=3777$ ) found that treating patients with severe COVID-19 with DEX increased the incidence of ICU-acquired respiratory tract infections (17.1% vs. 13.2%), regardless of illness severity at ICU admission or duration of invasive MV.<sup>[153]</sup> Lamouche-Wilquin et al.<sup>[154]</sup> concluded that early GC treatment increased ventilator-associated pneumonia (VAP) rates, which were associated with higher 90-day mortality. However, Gragueb-Chatti et al.<sup>[155]</sup> reported that preventive DEX dose did not increase VAP occurrence or bispectral index monitoring, and even led to longer VFD at day 28 (9 [0–21] days vs. 0 [0–11] days). Whether GCs increase VAP incidence remains uncertain, yet clinicians should attend to high VAP rates in patients with COVID-19-related ARDS who are treated with GCs. These cumulative data emphasize that careful immune monitoring is needed. In conclusion, early GC initiation ( $\leq 7$  days of symptom onset) should be avoided, and potential risks for nosocomial bacterial pneumonia and hyperglycemia should be considered.<sup>[156]</sup>

### GCs Therapy Side Effects

Two key issues limit the use of GCs as therapeutic agents. First, high-dose and/or long-term GCs use can cause adverse effects, including infections, hyperglycemia, cardiovascular disease, muscle weakness, and gastrointestinal bleeding. Second, glucocorticoid resistance (GCR) and CIRCI are usually observed, but underestimated, in patients who are critically ill. Because these issues can be devastating, clinicians must evaluate the potential risks before making decisions regarding GC treatment for ARDS.

### Infection

The increased risk of nosocomial infection in patients with ARDS from immunosuppression is a major concern. According to the ARDS Network,<sup>[112]</sup> the treated group had a lower probability of clinically diagnosed VAP, but it was difficult to determine how an undiscovered infection might affect the outcome due to the absence of infection surveillance. While several studies have found that GCs do not raise overall infection risk,<sup>[157,158]</sup> a meta-analysis showed a trend toward increased in-

cidence of new infections with increasing GC doses.<sup>[119]</sup> In addition, conflicting results have been reported, including infection risk increases in cohort studies (RR=1.35, 95% CI: 0.99 to 1.84) and decreases in RCTs (RR=0.83, 95% CI: 0.65 to 1.06).<sup>[114]</sup> It is unclear whether this difference can be attributed to the strict patient selection and infection monitoring procedures in RCTs. Higher incidences of ICU-acquired infections (45.8% vs. 35.2%) and pneumonia (41.0% vs. 26.4%) have been linked to GC treatment for influenza-induced ARDS.<sup>[115]</sup> A higher rate of hospital-acquired infections (HAP) (20% vs. 10%), primarily HAP/VAP but not bloodstream infections, was found among COVID-19 patients with GCs treated compared with placebo.<sup>[159]</sup> The CIBERESUCICOVID trial ( $n=4226$ ) reported an elevated incidence of both clinically diagnosed and microbiologically confirmed nosocomial bacterial pneumonia (odds ratio [OR]=1.29, 95% CI: 1.01 to 1.65) and hyperglycemia (OR=2.17, 95% CI: 1.35 to 3.48) in 3592 patients who received GCs.<sup>[152]</sup> Because early infection signs and symptoms can be masked by GCs, especially when insufficient infection surveillance measures are taken, infection rates vary. Future studies should define the timeframe for infection surveillance to more precisely define infection incidence in the context of clinical symptoms and etiological evidence, to provide prompt treatment.

### Hyperglycemia

Hyperglycemia is a common side effect of GCs and is evidenced by insulin resistance and impaired peripheral glucose uptake. Patients receiving GCs for pneumonia, sepsis, septic shock, or ARDS experience a marked rise in hyperglycemia, but not gastrointestinal bleeding, secondary infection, neuropsychiatric events, or cardiac events.<sup>[160-162]</sup> A group receiving methylprednisolone had a significantly higher incidence of hyperglycemia compared with a group receiving DEX.<sup>[163]</sup> Among patients with COVID-19, an episode of blood glucose concentration  $\geq 180$  mg/dL by post-admission day 3 occurred in 19% of patients in the DEX treatment group.<sup>[159]</sup> Because systemic GCs can increase hyperglycemia, their development may negate the benefits of GCs and impair prognosis in patients with COVID-19.<sup>[164]</sup> Hence, the appropriate GC therapy durations need to be determined, and intensive blood glucose monitoring is recommended.

### Muscle weakness and neuromyopathy

Muscle weakness is commonly observed in patients with ARDS who received MV for  $>7$  days. The ARDS Network showed conflicting results: a strong association between methylprednisolone and severe muscle weakness, and similar cases of neuromyopathy, between treated and placebo groups.<sup>[112]</sup> However, among patients with neuromyopathy, the treated group had a shorter median MV duration. Although 48-h continuous infusion of neuromuscular blocking agents did not raise the probability of ICU-acquired weakness,<sup>[165,166]</sup> the combination of GCs and neuromuscular blocking agents appeared to do so.<sup>[167]</sup> Increased blood glucose levels were considered to be associated with neuromuscular diseases.<sup>[168]</sup> GCs may protect against neuromyopathy in the intensive insulin therapy

setting.<sup>[169]</sup> The links among GCs, ICU-acquired neuromuscular dysfunction, and clinical outcomes remain unclear. Comprehensive electrophysiologic monitoring techniques for neuromuscular function will be required.

### GCR and CIRCI

Patients with ARDS and sepsis commonly progress to GCR, which can be acquired as a pathological host response to the ineffectiveness of endogenous GCs to modulate inflammation, endothelial function, and glucose metabolism,<sup>[170]</sup> or inherited via mutations in the *NR3C1* gene.<sup>[171]</sup> Since patients with severe sepsis and septic shock have blunted adrenal functions, low-dose GCs as an adjuvant therapy have become the standard treatment.<sup>[172]</sup> To achieve a higher benefit-to-risk ratio, guidelines regarding optimal dosage must be followed, along with strict monitoring to prevent and manage side effects.<sup>[134]</sup> Current therapeutic GCs do all activate GR activity, raising the potential for adverse effects.<sup>[173]</sup> To improve the therapeutic balance, more work should be done to stimulate the anti-inflammatory functions of GCs rather than unneeded functions.<sup>[173]</sup> Increased GC dosing may help to alleviate GCR, though overdose is a known danger.

CIRCI was first described, in 2008, as relative adrenal insufficiency, which occurs when the adrenal cortex is already fully activated to create substantial quantities of cortisol, but not enough to handle the extreme stress of illness; it is also termed “starvation in plenty.”<sup>[174]</sup> None of the total dose, highest dose, or length of GC therapy are reliable indicators of HPA axis recovery.<sup>[175]</sup> Since the publication of the guidelines for the diagnosis and management of CIRCI in 2017, prolonged low-dose GCs therapy has been recommended for survival benefits in patients with septic shock who are unresponsive to fluid resuscitation and moderate to high-dose of vasopressor therapy, but not in those without septic shock.<sup>[134]</sup> Because the negative effects of GCs are often dose-dependent, dose reduction may be an option for reducing side effects.

### Future Perspectives

ARDS is a heterogeneous syndrome with variable severity and underlying causes. To date, despite support therapies having been consistently proven beneficial, no specific pharmacotherapy agents have achieved concrete benefits. Clinical studies have demonstrated the potent anti-inflammatory and immunomodulatory effects of GCs in specific subgroups of ARDS. Nevertheless, overall mortality has not improved, especially following the COVID-19 pandemic. The complex interplay among efficacy, risk factors, and adverse events needs further consideration. Tailoring optimal treatment regimens by vigilantly monitoring the initial timeframe, dose, duration, drug selection, and tapering of GCs is of prime importance for improving outcomes in patients with ARDS. In the future, GC therapy in ARDS should be tailored according to personalized physiology and biology, as we move toward an era of precision medicine in critical illness. Global-scale collaboration—among academics, industry, regulatory agencies, sponsors, and patients—may help to reveal the benefits and potential risks of GC therapies in patients with ARDS.



## Author Contributions

**Yuanrui Zhao:** Writing – original draft, Writing – review & editing. **Zhun Yao:** Visualization. **Song Xu:** Writing – review & editing. **Lan Yao:** Writing – review & editing. **Zhui Yu:** Conceptualization, Writing – review & editing.

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## Ethics Statement

Not applicable.

## Conflict of Interest

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

## Data Availability

Data availability is not applicable to this study as no new data were created or analyzed in this study.

## Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jointm.2024.02.002](https://doi.org/10.1016/j.jointm.2024.02.002).

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