CORTICOSTEROID USE IN CRITICALLY ILL PATIENTS

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Abstract

The use of corticosteroids as immunosuppressants in critically ill patients is a very complex issue. These potent immunomodulators can be used in the treatment of critically ill patients with severe community-acquired pneumonia (SCAP) and/or septic shock. Local and systemic inflammatory responses are increased in SCAP, thus impairing gas exchange. Also, persistent inflammatory response is associated with higher mortality in patients with COVID-19 and non-COVID-19 ARDS (Acute Respiratory Distress Syndrome). However, the risk of administering systemic steroids (methylprednisolone, dexamethasone, hydrocortisone, etc.) to non-responders is evident. In general, the use of corticosteroids in critically ill patients should not be routine "one size fits all approach" but as personalized and individualized as clinically possible from "one size does not fit all" to "one size fits one".

Keywords: critically ill, septic shock, systemic corticosteroids, ARDS, COVID-19

Introduction

Corticosteroids are a class of hormones synthesized by the adrenal cortex. In 1855, Thomas Addison described the clinical signs of adrenal damage caused by tuberculosis and was the first to associate steroid hormone insufficiency with the condition. In 1948, Philip Hench used synthetically produced cortisone (compound E) in treating a patient with rheumatoid arthritis, marking the first known therapeutic application of corticosteroids. Since their discovery, these drugs have been used in practically every field of medicine and through nearly every method of administration[1]. Corticosteroids, which include glucocorticoids and mineralocorticoids, are synthetic analogs of natural steroid hormones synthesized by the adrenal cortex. Synthetic hormones differ in their levels of glucocorticoid and mineralocorticoid activity. Glucocorticoids play a vital role in metabolism and possess immunosuppressive, anti-inflammatory, and vasoconstrictive properties. Mineralocorticoids control the balance of electrolytes and water by influencing ion transport in the epithelial cells of renal tubules[2]. In practice, however, corticosteroids usually refer to glucocorticoids. Glucocorticoids are key stress hormones that regulate a range of physiological functions essential for survival[3]. Nevertheless, the use of steroids in modern intensive medicine remains controversial. While various benefits of corticosteroid use are cited, they often lack sufficient evidence. It is important to note that steroids are potent hormones with a wide range of both physiological effects and adverse consequences. Therefore, these drugs can have a significant impact on critically ill patients, both positive and negative[4].

Mechanism of action of corticosteroids

Corticosteroids act through a variety of mechanisms. In general, they have anti-inflammatory and immunosuppressive effects, protein and carbohydrate metabolism effects, water and electrolyte effects, central nervous system as well as blood cell effects[1, 2]. Steroid hormones are lipophilic substances that are generated in one cell and may travel long distances inside the body to trigger biological responses in another cell. Steroid hormones are lipophilic substances produced in one cell that can traverse a lengthy journey through the body to elicit biological responses in another cell. The interaction of a steroid hormone with a nuclear receptor (NR), typically in the cytoplasm, leads to conformational changes in the receptor and translocation into the nucleus; there, interaction with specific DNA (Deoxyribonucleic Acid) sequences occurs, regulating transcription. In addition to the traditional genomic mode of action, alternative mechanisms of steroid activity have emerged, involving rapid, non-genomic communication. The subcellular site of initiation of steroid hormone activity distinguishes between these two primary modes of action, which are not mutually exclusive but can influence each other[5]. The glucocorticoid receptor serves as the mediator of the genomic

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mode of action, leading to most of the anti-inflammatory and immunosuppressive effects[6]. The non-genomic pathway is faster and is driven by interactions between intracellular or membrane-bound glucocorticoid receptors. Within seconds to minutes of receptor activation, a cascade of reactions occurs, including the inhibition of phospholipase A2, which is necessary for the production of inflammatory cytokines, for example. The adrenal cortex has three layers that secrete different hormones: 1) *Zona glomerulosa* produces mineralocorticoids (aldosterone); 2) *Zona fasciculata* produces glucocorticoids (cortisol); 3) *Zona reticularis* produces sex hormones. Mineralocorticoids regulate water and electrolyte balance, while glucocorticoids have anti-inflammatory, immunosuppressive, and metabolic properties. It's important to always consider that all corticosteroids have varying degrees of mineralocorticoid properties. Therefore, patients should be carefully monitored for water and salt retention, as well as potassium excretion, when corticosteroids with significant mineralocorticoid activity are administered. Systemic glucocorticoids include prednisone, methylprednisolone, dexamethasone, and hydrocortisone, among others. Mineralocorticoids include fludrocortisone and 11-deoxycorticosterone (Deoxycorticosterone, DOC), which is a precursor to aldosterone. The zona glomerulosa is the outer layer of the adrenal cortex and is the only part of the adrenal gland that contains the enzyme aldosterone synthase (CYP11B2). As a result, only cells in this zone are a source of aldosterone. Cells in the *zona reticularis* synthesize androgens, such as dehydroepiandrosterone (DHEA) and androstenedione, from cholesterol.

Effects of corticosteroids on host immune response

Essentially, all immune cells originate from the same multipotent hematopoietic stem cell called hemocytoblast. From it, two distinct cellular lineages emerge the myeloid lineage and the lymphoid lineage. Common myeloid progenitor cells give rise to megakaryocytes (precursors of platelets), erythrocytes, mast cells, and myeloblasts. Myeloblasts are unipotent stem cells that can differentiate into basophils, neutrophils, eosinophils, and monocytes (which are termed macrophages after migrating from circulation into various tissues). On the other hand, common lymphoid progenitor cells give rise to large granular lymphocytes (natural killer cells) and small lymphocytes (T lymphocytes and B lymphocytes, which can differentiate into plasma cells capable of producing and releasing immunoglobulins). This division of cell lineages largely overlaps with the two types of immune systems: innate (various granulocytes, monocytes) and acquired immune response (lymphocytes). The innate immune system is pre-existing, inherited, fast, fights against everything (non-specific), always active, moderately potent, and lacks memory. In contrast, the acquired immune system develops after exposure, is slower, specific, normally inactive, highly potent, and has memory. Specific functions of the innate immune system primarily involve triggering a cytokine response, activating the complement system, and attracting immune cells to the site of infection. The goal is to achieve and facilitate phagocytosis by phagocytic cells through opsonization (marking and coating bacteria with opsonins), capturing, ingesting, and degrading these foreign particles. Another distinct function of the innate immune system is antigen presentation, mediated by antigen-presenting cells (APCs). For instance, APCs present a piece of the bacteria or virus to a T lymphocyte. If that does not happen there is no adaptive immune response. When it does happen, T lymphocytes differentiate into cytotoxic T cells or CD4+ T helper (Th) cells. Also, the T cells can stimulate the B cells to differentiate into plasma cells producing antibodies and memory B cells. Of particular interest are uncommitted CD4+ Th cells. They can differentiate into two pathways which are characterized by a specific set of cytokines that they secrete. Th1 cells produce pro-inflammatory cytokines, like interferon IFN-γ, etc. and they are instrumental for fighting intracellular pathogens; on the other hand, Th2 cells produce anti-inflammatory cytokines, like interleukin (IL)-4 etc. and they orchestrate immune response to large extracellular pathogens[7].

Corticosteroids suppress many immune processes. Generally speaking, these effects are less pronounced. In terms of innate immunity, apoptosis and recognition (recognition) are less pronounced, and in terms of acquired immunity, there are fewer T cells, and they produce fewer cytokines. Regarding B cells, it appears that corticosteroids do not affect their number, but B cells produce fewer immunoglobulins (antibodies). The Major Histocompatibility Complex (MHC) represents a group of proteins on the cell surface that are crucial for the ability of the acquired immune response to identify foreign substances. On the surface of most immune cells, including monocytes/macrophages, dendritic cells, and B cells, there is HLA-DR (Human Leukocyte Antigen D-Related), which belongs to MHC class II proteins. The expression of HLA-DR is associated with immune cell activation as well as antigen presentation, which triggers the acquired immune response. Low expression of HLA-DR, on the other hand, is associated with an anti-inflammatory phenotype. Several factors regulate the expression of HLA-DR on immune cells, such as proinflammatory mediators like IFN-γ and anti-inflammatory mediators like IL-10. It's crucial to note that some drugs, such as corticosteroids and catecholamines, can also suppress the expression of HLA-DR. Since the expression of HLA-DR on monocytes (monocytic HLA-DR, mHLA-DR) represents a fundamental link between innate and acquired immune responses, the important interaction between monocytes and T cells is also referred to as the "immune synapse".

Corticosteroids in the treatment of critically ill patients with severe community-acquired pneumonia and septic shock

In patients with life-threatening acute respiratory failure due to severe community-acquired pneumonia (SCAP), invasive mechanical ventilation (IMV) may be necessary. In an interesting study involving 370 patients with severe community-acquired pneumonia, it was shown that if there was no shock or IMV, the mortality rate was 16%; if these patients developed shock alone, the mortality rate increased to 25%; if these patients underwent IMV alone, the mortality rate was 30%; and if patients with severe community-acquired pneumonia developed shock and required IMV, the mortality rate was 38%[9].

This spectrum of increasing mortality rates from severe community-acquired pneumonia to an unacceptable almost 40% has necessitated multimodal therapeutic approaches, including the use of immunomodulatory drugs. In the treatment of severe community-acquired pneumonia, over the years, there have been attempts to implement anti-inflammatory therapy, which has included corticosteroids, macrolides, statins, and immunoglobulins[10]. While antibiotics can relatively quickly eliminate pathogens from the respiratory system, continuous hyperinflammation may be responsible for an increased mortality rate. Therefore, there are multiple arguments for the use of corticosteroids in the treatment of severe community-acquired pneumonia. Local and systemic inflammatory responses are heightened in this condition, which disrupts gas exchange across the alveolar-capillary membrane. Additionally, the persistent inflammatory response is associated with increased mortality. In some patients with severe community-acquired pneumonia, there is adrenal insufficiency that increases systemic inflammation. Therefore, corticosteroids could potentially be used to suppress both local (lung) and systemic inflammatory responses. It's important to note that, according to the latest guidelines from 2019, the use of corticosteroids in the treatment of severe community-acquired pneumonia is not recommended[11].

However, in the guidelines for the diagnosis and treatment of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients, there is a conditional recommendation to use a daily intravenous dose of < 400 mg of hydrocortisone for a duration of 5 to 7 days in hospitalized patients with community-acquired pneumonia[12]. An interesting randomized clinical study included only patients with severe community-acquired pneumonia and pronounced systemic inflammatory response (assessed by a cut-off value of C-reactive protein > 150 g/L)[13]. Methylprednisolone was administered for five days at a dose of 0.5 mg/kg/12 h and was discontinued without tapering to lower doses. Treatment success was significantly higher in the group of patients receiving methylprednisolone compared to the placebo group that did not receive it. The study authors concluded that adjunctive use of corticosteroids should be supported in this specific patient population. This therapeutic approach is not suitable for every patient; for instance, corticosteroids should not be administered if the causative agent of severe community-acquired pneumonia is a type of influenza virus. Therefore, it's important to note that corticosteroid use in patients with influenza can increase the mortality rate. One of the recent meta-analyses has shown that corticosteroids can reduce mortality rates in patients with COVID-19 and acute respiratory distress syndrome (ARDS)[14].

The latest meta-analysis on the use of corticosteroids in patients with community-acquired pneumonia, published in March 2023, demonstrated an association between corticosteroid use and a reduced risk of disease progression to the need for mechanical ventilation in hospitalized patients with community-acquired pneumonia. However, there was no association between corticosteroid use and treatment success rates or mortality rates[15].

The choice of corticosteroid administered to patients with severe community-acquired pneumonia is important. A meta-analysis of the effectiveness and safety of adjunctive corticosteroid use in this patient population showed that the type of corticosteroid used was a key factor in reducing the mortality rate. While the use of prednisolone or methylprednisolone reduced the mortality rate, the use of hydrocortisone did not. Therefore, the authors of this meta-analysis concluded that it is not a class effect and that hydrocortisone should not be used in patients with severe community-acquired pneumonia[16]. The anti-inflammatory effect is more pronounced with the use of methylprednisolone, dexamethasone, or prednisolone. In the scientific literature, there are conflicting results regarding the use of corticosteroids in patients with severe community-acquired pneumonia. For example, the latest study published in March 2023 demonstrated that critically ill patients with severe community-acquired pneumonia who received hydrocortisone in their treatment had a higher likelihood of survival compared to the placebo group[17]. The importance of individualizing the use of corticosteroids in therapy is emphasized in an interesting study where patients with community-acquired pneumonia were divided into four subgroups based on the level of inflammation (high or low; assessed by IL-6, IL-8, and C-reactive protein values) and cortisol levels. Patients received either 50 mg of prednisone or a placebo for five days. The best effect of corticosteroids was achieved in patients with high levels of cytokines regardless of cortisol levels[18]. Therefore, the dilemma regarding the choice of corticosteroids has not been resolved yet.

Generally, it appears that patients with severe community-acquired pneumonia who develop shock could benefit from corticosteroid therapy. However, the risk of steroid use in the non-responder subgroup is evident. Steroid resistance may exist in patients with respiratory infections. The indications and desired effects of corticosteroids

include their anti-inflammatory properties, suppression of the host's immune response, and limitation of lung hyperinflammation. On the other hand, severe adverse effects include immunosuppression and opportunistic infections (fungal, viral, etc.), disrupted glucose metabolism, and peptic ulcers. There are several potential mechanisms of glucocorticoid resistance. Context-independent factors include genetics (including glucocorticoid efflux and hereditary mutations and polymorphism of the glucocorticoid receptor) and post-translational modifications of the glucocorticoid receptor. Context-dependent mechanisms of glucocorticoid resistance involve the cellular microenvironment, cytokines, oxidative stress, and possibly hypoxia.

In summary, corticosteroids reduce mortality in patients with severe community-acquired pneumonia who develop shock. This therapeutic approach also increases the number of days without invasive mechanical ventilation (reduces disease progression to the need for IMV). Further research is necessary to explore the phenotypes and genotypes of patients who would benefit the most from corticosteroid treatment. Corticosteroid resistance could potentially explain the heterogeneity in treatment outcomes.

Corticosteroids in ARDS treatment

There are several clinical questions related to the use of corticosteroids in patients with ARDS, regardless of the etiology. It is not clear how sensitive these patients are to the effects of steroids. It has been shown that thromboinflammation and acute fibrinous and organizing pneumonia (AFOP) are more common in COVID-19 than in influenza. Additionally, COVID-19 is not the same disease as it was at the beginning of the pandemic. Significant changes in immunogenicity have occurred from the initial variant to the currently active virus strains; there is a higher contagion rate, but a lower risk of developing severe ARDS. Immunovasculopathy is less frequently present in COVID-19-associated ARDS today.

Guidelines for the use of corticosteroids in ARDS are conflicting. The guidelines that support the use of corticosteroids could be dependent on meta-analyses that may be biased. British guidelines for ARDS therapy suggest that the role of corticosteroids might be more of a research recommendation, and that multicenter, randomized controlled trials with adequate study power and long-term patient follow-up are needed. The American Thoracic Society (ATS) in its 2019 guidelines for the treatment of community-acquired pneumonia, one of the common causes of ARDS, does not recommend the use of corticosteroids in the absence of septic shock. It's important to note that this recommendation is conditional and based on evidence of moderate quality. Diffuse Alveolar Damage (DAD) is a key histological feature of ARDS. The early phase is exudative, characterized by interstitial and intraalveolar edema; hyaline membranes are present, along with hyperplasia of type II pneumocytes, intra-alveolar hemorrhage, and mononuclear cell infiltrates. The late (proliferative) phase (> second week) is characterized by pronounced fibroblast proliferation in both interstitial and intraalveolar spaces; there is hyperplasia of type 2 cells and thrombi in small pulmonary arteries. Dexamethasone could have a more favorable effect in patients with ARDS compared to other corticosteroids due to its pronounced potency, extended duration of action, and weak mineralocorticoid effect. An interesting study was conducted in 2020 on non-COVID-19 ARDS patients, randomized into two groups: the study group received dexamethasone immediately, while the control group received standard treatment. Patients in the study group received an intravenous dose of 20 mg of dexamethasone once daily from the first to the fifth day; after that, the dose was reduced to 10 mg once daily from the sixth to the tenth day. The primary goal was to determine the number of days without invasive mechanical ventilation within the 28-day treatment period[19]. The authors demonstrated that the hospital mortality rate (24% *vs* 36%), as well as overall mortality after 60 days (21% *vs* 36%), were lower in the group of patients treated with dexamethasone. The latest meta-analysis of corticosteroid use in the treatment of COVID-19 and non-COVID-19 ARDS was published in 2021. It included 18 randomized controlled trials with a total of 2.826 patients, and it was shown that corticosteroid use likely reduced the mortality rate in patients with ARDS of any etiology. This beneficial effect of corticosteroids was observed in both non-COVID-19 and COVID-19 ARDS patients. Patients who received corticosteroids for a longer duration (over a week) had better survival compared to patients who received this therapy for a shorter period[20]. It could be summarized as follows: there is no evidence to support the use of high doses of methylprednisolone in the acute phase of ARDS; moderate doses of methylprednisolone have not shown benefit in the treatment of persistent ARDS, and even led to an increased mortality rate if initiated more than two weeks after the onset of ARDS. Studies have indicated some improvement in lung function in response to the administration of low doses of methylprednisolone. As for dexamethasone, its use in ARDS therapy could be considered. However, these results are not yet sufficient to change clinical practice, meaning that routine use of dexamethasone in patients with ARDS is still not supported.

Systemic corticosteroid therapy in critically ill patients

Severe COVID-19 has become a major focus of corticosteroid therapy. Key pathophysiological events in this viral sepsis include: 1) Endotheliopathy - endothelitis, resulting in diffuse excessive inflammation affecting various organs; 2) Immunothrombosis specific to this viral sepsis. Systemic corticosteroids reduce neutrophil oxidative burst capacity and their presence at the site of infection and inflammation. When comparing standard therapy to systemic corticosteroid administration and standard therapy without

it, there is a clear signal of benefit from systemic corticosteroid use in the treatment of patients with severe and/or critical COVID-19. Systemic corticosteroids reduce mortality rates and improve organ function in these patients[21-24]. Dexamethasone is administered in moderate doses ranging from 6 to 12 mg, with an average duration of 10 days in the treatment of patients with severe and/or critical COVID-19. The use of dexamethasone has reduced the mortality rate in patients requiring oxygen support or invasive mechanical ventilation. However, this does not apply to patients who do not require additional oxygen. Therefore, patients with COVID-19 who do not need respiratory support do not need corticosteroid therapy. In the treatment of patients with severe and/or critical COVID-19, low doses of hydrocortisone (200 mg daily) or a range of 50 mg to 100 mg every 6 hours for one week can be used. There is no difference in the choice of corticosteroid; they all work by alleviating inflammation. The addition of anti-IL-6 drugs to corticosteroid therapy for patients with the most severe forms of COVID-19 has shown significant benefits[25, 26]. In patients who received both tocilizumab and corticosteroids, the mortality rate was reduced in two major studies, RECOVERY and REMAP-CAP. Additionally, analyses have shown that the use of tocilizumab alone is detrimental, indicating that there is an interaction between corticosteroids and tocilizumab that is beneficial for patients[27]. Therefore, it should be emphasized that IL-6 antagonists should only be administered in patients with COVID-19 who are already receiving corticosteroids[28, 29]. Corticosteroid therapy in patients with severe and/or critical COVID-19 has proven to be highly effective.

Another indication for intravenous systemic corticosteroid administration is septic shock in critically ill patients. According to the 2021 Surviving Sepsis Campaign guidelines, intravenous corticosteroid therapy is recommended for patients with septic shock requiring vasopressor therapy. This conditional recommendation is based on moderate-quality evidence[30]. This represents an improvement compared to previous guidelines where the recommendation was also conditional but based on low-quality evidence. Essentially, when there is no response to other interventions (i.e., volume resuscitation and vasopressor support), intravenous hydrocortisone administration is recommended at a dose of 200 mg per day, divided into 4 doses of 50 mg every 6 hours or as a continuous infusion. It is also suggested to initiate this therapy when the dose of norepinephrine or epinephrine reaches ≥ 0.25 μg/kg/min for at least four hours from the onset of maintaining the desired mean arterial pressure. All the knowledge about systemic and compartmentalized immune responses holds significant clinical importance. For instance, a few years ago, it was demonstrated that cytokine levels in plasma are predictors of the response to corticosteroid therapy in patients with septic shock[31]. Researchers found that the survival benefit of corticosteroid therapy depends on the levels of cytokines in the plasma. In patients with septic shock, several cytokines, including IL-6 and IL-4, were measured, and their threshold values were determined. The highest survival rates were observed in patients whose cytokine levels were below the threshold values and who did not receive corticosteroid therapy because it was not needed. Slightly lower survival rates were seen in patients whose cytokine levels were above the threshold values and who received corticosteroid therapy because it was necessary. On the other hand, poorer survival outcomes were observed in patients with cytokine levels below the threshold values who still received unnecessary corticosteroid therapy, leading them into immunosuppression. Ultimately, the worst survival rates were found in patients with cytokine levels above the threshold values who did not receive corticosteroid therapy when it was needed, indicating excessive hyperinflammation in this subgroup of septic shock patients. The imbalance between proinflammatory and anti-inflammatory cytokines not only contributes to the immunopathogenesis of sepsis and septic shock but can also guide therapy decisions. A recent exploratory data analysis from the CORTICUS (Corticosteroid Therapy of Septic Shock) study revealed that a low serum IFN-γ/IL-10 ratio is a predictor of better survival in the group of patients treated with hydrocortisone, while a high ratio is a predictor of better survival in the placebo group[32]. Therefore, the IFN-γ/IL-10 ratio could serve as a useful molecular marker to guide the potential use of hydrocortisone in patients with septic shock.

However, patients with bacterial sepsis and severe COVID-19 (viral sepsis) are highly heterogeneous, exhibiting different phenotypes. Additionally, determining the exact immune profile for each patient is not feasible in clinical practice due to significant inter- and intra-individual variations. Hence, implementing appropriate immunomodulatory therapy, including corticosteroid therapy, is challenging. Therefore, individualized therapy is recommended; if corticosteroids are administered too early or too late in the course of the illness, they can have detrimental effects. An interesting study demonstrated that the use of corticosteroids in older critically ill patients with COVID-19 significantly increased the 30-day mortality rate (42% in the group without corticosteroids compared to 53% in the group with corticosteroids)[33]. Since corticosteroid therapy is routinely administered to critically ill patients with COVID-19, it has been observed that approximately 50% of them develop hospital-acquired infections, with ventilator-associated pneumonia (VAP) being the most common type, accounting for around 50% of cases[34]. However, at the beginning of the pandemic, when critically ill patients with COVID-19 were not receiving corticosteroid therapy, the authors of an interesting study investigated the impact of dexamethasone administration on the incidence of ventilator-associated pneumonia (VAP) in those patients[35]. VAP developed in 63% of patients who received dexamethasone in their therapy and in 57% of those who were not treated with dexamethasone. The authors concluded that the administration of dexamethasone was not associated with an increased incidence of VAP. It should be noted that this study was retrospective and had

a small number of included patients. Another study, focusing on the same issue, included more than 300 patients and showed that the incidence of VAP in the dexamethasone group was 56%, compared to 35% in the group without dexamethasone, which was statistically significantly lower[36]. Additionally, in the dexamethasone group, sepsis developed in 28% of patients, and shock occurred in 24%. In contrast, in the group without dexamethasone, only 13% of patients developed sepsis and 20% developed shock. One approach to addressing this issue is to focus on subgroups of patients with COVID-19 ARDS, where different responses to corticosteroid therapy have been identified through latent class analysis[37]. Researchers have identified hypo-inflammatory and hyper-inflammatory subphenotypes of ARDS, as well as two classes of COVID-19 ARDS based on selected variables. Patients with Class 2 COVID-19 ARDS are similar to the hyper-inflammatory subphenotype of ARDS and benefited from corticosteroid therapy, which reduced the mortality rate. Patients with Class 1 COVID-19 ARDS are similar to the hypo-inflammatory subphenotype of ARDS, and their mortality rate increased when treated with corticosteroids. In summary, critically ill patients with COVID-19 are at a high risk of developing VAP. This risk can be further increased by corticosteroid therapy in certain patients. In the future, personalized therapy research would facilitate decision-making on the risk-benefit ratio for each patient. Reactivation of viruses is another real danger in critically ill patients treated with immunosuppressants such as corticosteroids. In this regard, attention should be focused on the BK virus (Human polyomavirus 1), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus (HHV), human polyomavirus 2, also known as JC virus, as well as many other viruses.

Conclusion

The use of corticosteroids as immunosuppressants in critically ill patients is highly complex. These potent immunomodulators can be employed in the treatment of critically ill patients with severe community-acquired pneumonia and/or septic shock. Additionally, persistent inflammatory response is associated with increased mortality in patients with both COVID-19 and non-COVID-19 (ARDS), making the role of corticosteroids crucial. The application of immunosuppressive corticosteroid therapy in critically ill patients should not follow a routine “one-size-fits-all“ approach but rather should be as personalized and individualized as clinically feasible, ranging from a “one-size-fits-none“approach to a “one-size-fits-one“ approach.

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