Chapter

Corticosteroids in Emergency Pathologies

Miroslav Radenković and Ivana Milićević

Abstract

Ever since their discovery in the fifties of the last century, as an anti-inflammatory drugs for the treatment of rheumatoid arthritis, corticosteroids have found a significant place and wide application in various fields of medicine. Their effects are known to be diverse. The most significant ones are the anti-inflammatory, anti-allergic, and immunosuppressive effects. Furthermore, they affect the hematopoietic system. Corticosteroids produce complex metabolic effects by stimulating glyconeogenesis, increasing the uptake of amino acids in the liver and kidneys, and enhancing lipolysis. Given that natural adrenocortical hormones are synthesized under the influence of stress, it is expected that in the emergency situations, where we face vitally endangered patients whose body is under the stress due to respiratory insufficiency or impaired hemodynamics, corticosteroids do have significant place in the treatment. Thus, these drugs are used in the treatment of acute exacerbation of chronic obstructive pulmonary disease and asthma, in anaphylactic reactions, spinal shock, Addisonian crisis, and sepsis. During the COVID-19 pandemic, corticosteroids found their place in certain stages of treatment, as well as in many national protocols for the treatment of COVID-19 patients. Hence, the use of corticosteroids in the emergency pathologies will be reviewed in this chapter.

Keywords: corticosteroids, COPD, asthma, Addisonian crisis, anaphylaxis, sepsis, COVID-19

1. Introduction

From their first discovery, in the fifties of the last century, as anti-inflammatory drugs for the treatment of rheumatoid arthritis, corticosteroids have found a significant place and wide application in various fields of medicine. Natural adrenocortical hormones are steroid molecules that are released from the cortex of the adrenal gland and have numerous physiological functions. These include: (1) glucocorticoids (cortisol), (2) mineralcorticoids (aldosterone), and (3) androgens (dehydroepi-androsterone). Today, numerous synthetic derivatives of natural corticosteroids have been developed, with some enhanced or oppositely reduced pharmacological properties. Glucocorticoids show significant metabolic, anti-inflammatory, immunosuppressive, and vasoconstrictor effects. On the other hand, mineralcorticoids regulate the level of water and salt in the body, help the reabsorption of Na^+ from the kidney tubules, and increase the excretion of K^+. Nevertheless, when we consider the practical application of corticosteroids in various pathological conditions, we usually think of glucocorticoids.

The circadian rhythm of glucocorticoids is influenced by the negative feedback loop of the hypothalamus-pituitary-adrenal cortex. These steroid hormones are synthesized from cholesterol. They achieve their physiological and pharmacological effects through the intracellular glucocorticoid receptor [1]. Initially, they diffuse through the cell membrane and bind to a receptor located on a specific protein. Afterward, this entire complex enters the nucleus and causes the expression of certain genes, responsible for the synthesis of specific proteins. This represents a gene-related and time-consuming mechanism of action. There is also another, faster way of producing the effect, where the glucocorticoid binds to the receptor in the cytoplasm, where protein synthesis is not required, and the effect is achieved after a few minutes of binding to the receptor.

The physiological and pharmacological effects of glucocorticoids are diverse. The most significant ones are related to anti-inflammatory, anti-allergic, and immunosuppressive effects. Consequently, they affect the hematopoietic system, increasing the number of neutrophils while simultaneously decreasing the number of lymphocytes, monocytes, eosinophils, and basophils. They antagonize the effect of vitamin D on the absorption of calcium from the digestive tract. To continue, they stimulate the secretion of hydrochloric acid. These drugs have complex metabolic effects as well, thus stimulating gluconeogenesis, increasing the uptake of amino acids in the liver and kidneys, and enhancing the lipolysis. They also cause catabolic effects in lymphoid and connective tissue and muscles, as well.

Due to the wide range of described effects, a large number of different pathological conditions can be identified where these drugs may be used, including various methods of administration (oral, intravenous, and inhalation). Given that natural adrenocortical hormones are usually synthesized under the influence of stress, in cases where the hypothalamus was stimulated, this endocrine structure releases corticotropin-releasing factor (CRF). Consequently, the pituitary gland releases corticotropin (ACTH) and leads to the release of cortisol, which finally starts a cascade of metabolic processes to overcome the stress. It is expected that in the emergency situations with vitally endangered patients, whose body is under the stress due to the respiratory insufficiency or impaired hemodynamics, the corticosteroids will certainly have an important place in the treatment.

These drugs are used in the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD) and asthma, in anaphylactic reactions, in spinal shock, and in Addison's disease and related crisis. According to the guidelines for the treatment of sepsis and septic shock from 2017, as well as the revised recommendations from 2021, the corticosteroids are included in the treatment of this serious and urgent condition [2]. During the COVID-19 pandemic, corticosteroids have found their place in certain stages of treatment and were accordingly included in many national protocols for the treatment of COVID-19-positive patients.

In the further segments of this chapter, the most important indications for using glucocorticoids in the emergency pathologies will be addressed.

2. Acute exacerbations of chronic obstructive lung disease

Chronic obstructive pulmonary disease (COPD) is characterized by limited (reduced) airflow in the airways. The obstruction is progressive and related to the inflammatory process caused by harmful particles and gases from the external environment. Smokers and mostly people over 40 years of age were linked to the COPD.

It is the third most common cause of death in the world and the seventh cause of reduced overall health ability [3]. According to data from the World Health Organization (WHO) from 2011, only in the USA, there were about 13 million adults being treated from the COPD [4]. The main symptoms of COPD include choking, coughing, and expectoration of the purulent contents. Acute exacerbation of the disease obligatory implies the need for the additional therapy and in some cases hospitalization, and it clearly affects the progression of the disease and mortality. Exacerbations of COPD are most often associated with infection, inhalation of air pollution, and the influence of other chronic diseases that the patient is suffering from. Given the heterogeneity of the disease exacerbation causes, the basic form of COPD treatment is related to the causal therapy against the causative agent, modulation of the overall body's response, and the maintenance of the patient's respiratory and hemodynamic status.

Corticosteroids are present in all protocols for the treatment of acute COPD, but determining the most effective dose and duration of therapy is still a subject of research. They are used as intravenous, oral, and inhalation therapy. They improve ventilation and gas exchange, as shown by pulmonary function tests; also reduce dyspnea; and, finally, speed up the recovery and duration of hospital treatment.

Systemic corticosteroids have been the standard therapy in COPD exacerbations for many years. Of course, long-term use of glucocorticoids is an independent risk factor for increased mortality in patients with COPD. This is mainly due to a number of possible side effects and the impact of therapy on associated diseases. The *Reduce* study showed that the therapy with 40 mg of prednisone intravenously for 5 days was as effective as 14-day therapy in terms of repeated exacerbations [5]. The latest guidelines of the European Respiratory and American Chest Association favor a shorter treatment period (less than 14 days) and emphasize the use of oral preparations over the systemic ones. Even for patients who are hospitalized for the treatment of exacerbations, a short-term oral therapy is recommended [6]. Several studies have shown better efficacy of short-term therapy, as well as favorable pharmacokinetics of this type of treatment, which enables adequate drug bioavailability. In addition to systemic and oral therapy, inhalation therapy with corticosteroids, in combination with long-acting bronchodilators, was shown to be effective, too [7].

Today, clinicians are turning to the latest guidelines from the *GOLD* study, which represents the Global Strategy for the Diagnosis, Treatment, and Prevention of COPD, revised in 2019 [8]. The *GOLD* study emphasizes an individual approach, based on the severity of symptoms, risk of exacerbation, comorbidities, adverse effects, response to therapy, and availability of medication. This is precisely why the number of eosinophils is determined for each patient, because the anti-inflammatory effect of corticosteroids depends on how much inflammation plays a role in the pathogenesis of the disease. Recent studies have shown that the number of eosinophils is a direct predictor of the effectiveness of corticosteroids in preventing future exacerbations. Therefore, an individual pharmacological treatment plan must be applied for each patient, both for the disease and for an emergency, such as an exacerbation, still based on comorbidities, severity of symptoms, risk of side effects, hemodynamic, and respiratory status.

3. Acute asthma exacerbations

Asthma is a chronic inflammation of the airways that causes their hypersensitivity to various factors from the external environment. In fact, they provoke a narrowing of the airways, which in turn causes discomfort in the form of a feeling of shortness

of breath, coughing, and wheezing in the chest. The disease can occur in young children, and it can also develop in the elderly. There are numerous causes, recognized as external and internal ones. The external ones include air pollution, allergens in the air, pollen, industrialization, internal genetic predisposition, a diet with use of additives, maternal smoking during pregnancy, and so on. All these factors lead to airway inflammation, further increased mucus production, airway wall remodeling, and bronchial hypersensitivity. Given that inflammation has a key role in the pathogenesis of the disease, the main goal in the treatment of asthma is to control the symptoms and signs of inflammation in order to avoid future exacerbations.

An acute asthma attack is an episode of progressive suffocation, shortness of breath, coughing, and wheezing in the chest. According to some authors, an acute asthma attack is one specific condition that requires the use of systemic corticosteroids [9].

It has been established that corticosteroids reduce inflammation in the airways. They are most commonly used in the form of inhalation preparations in the chronic therapy of asthma as well as systemically when needed in severe exacerbation episodes. The recommendation in all guidelines for the treatment of acute asthma attack is to repeat the inhaled dose of a drug and if there is no improvement, to introduce systemic therapy. As with COPD, the preference is given to oral preparations, 50 mg of prednisolone for 5–7 days [10]. As previously confirmed, a short-term treatment is considered to be more effective [11]. It is recommended to introduce the oral preparation in the first hour of the attack. Oral preparations are recommended in exacerbations, as well as maintenance therapy in patients with a severe form of the disease, which accounts for about 10% of patients. Of course, the use of oral and systemic corticosteroids can be associated with a number of side effects. This is why the recommendations direct us to use systemic corticosteroids only for 5–7 days during acute exacerbation. In a large cohort study, Vorham et al. [12] showed that the use of oral corticosteroids in Great Britain is far higher than recommended, in terms of doses (more than 7.5 mg/dL) and duration of administration, wherein the excessive administration was explained by the low price of these drugs.

A special form of exacerbation of the disease is the status asthmaticus, a vitally threatening condition with hypoxia, hypercapnia, and a high risk of developing acute respiratory insufficiency. The recommendation for the treatment of this condition is, in addition to oxygen support, bronchodilators and 125 mg methylprednisolone intravenously [13].

Finally, it has to be underlined that in addition to unwanted effects of corticosteroids, there is also a problem of effectiveness in some patients, in the sense that not all patients have a good therapeutic response, which means that an individual approach is needed. Therefore, the balance between the efficacy and safety of therapy must be established for each and every patient.

4. Anaphylaxis

Anaphylaxis is a severe allergic reaction, which has a rapid onset and development of symptoms and can cause an anaphylactic shock with a possible fatal outcome. Allergic reactions can be induced by medicines, food ingredients, insect bites, and so on. Visual changes rapidly occur at the point of an allergen entry, followed by itching, urticaria of the skin, angioedema, bronchospasm, rhinorrhea, gastrointestinal disorders, a drop in arterial tension, and, if not responded to in time, an overall shock. The first step in treatment would be to administer epinephrine.

Glucocorticoids are often given in anaphylaxis, but there is a little evidence of their effectiveness. Due to the specific mechanism of action, which includes intracellular position of the respective receptors, their effect may take several hours to be fully developed. So, these drugs would not be able to act on the initial signs and symptoms of anaphylaxis. However, one of the reasons for their widespread use in this disorder is to prevent the second (so-called protracted) phase of an anaphylactic reaction, which sometimes may exist or occur even after several hours. Nonetheless, in the recent literature, there are several studies that did not confirm the previous notion. Hence, the use of glucocorticoids can be possibly justified in patients who are hospitalized for anaphylaxis, in order to further prevent bronchospasm, or who are already being treated from COPD and asthma.

In 2021, the Resuscitation Council of Great Britain published the new guidelines for the care and treatment of anaphylaxis that support the complete exclusion of the use of glucocorticoids. There was reportedly little evidence to support that glucocorticoids prevent the delayed response. In some studies, it has even been shown that the use of these drugs was associated with greater mobility, or increased hospitalization, in the case of prehospital administration. The explanations suggested that perhaps the administration of glucocorticoids actually delayed the administration of epinephrine, which should be the first drug of choice in this case [14, 15].

5. Spinal shock

Spinal shock, occurring after spinal cord injury, is a special pathological condition characterized by the loss of all neurological activity below the level of injury. These would include the loss of motor, sensory, reflex, and autonomic functions. It starts 30–60 minutes after the spinal cord injury and can last up to 6 weeks after the injury. It can lead to permanent disability.

Until recently, methylprednisolone was widely used in the early stages of treatment after the spinal cord injury, namely, in the first 8 hours. In recent years, more and more studies have shown that there is no difference between patients that received methylprednisolone and the placebo group, especially in terms of the motor response. The side effects are unfortunately numerous [16]. In animal models, the follow-up studies provided specific evidence at the molecular level, as well. Thus, Nelson et al. [17] showed in their research using a fish model that glucocorticoids inhibited neuron regeneration by directly acting on ependymal glial cells, independently of microglia.

Considering the severity of the clinical presentation that exists in a spinal cord injury, as well as a series of side effects related to corticosteroids, more studies are needed to examine the exact relationship between the risks and benefits of using these drugs in this specific condition.

6. Addisonian crisis

Addison's disease is a rare chronic condition that occurs when the adrenal glands are unable to provide sufficient amounts of hormones (glucocorticoids, mineralocorticoids, and androgens). Consequently, therapeutic hormone replacement is necessary. Addison's disease is also called primary adrenal insufficiency. Given that quoted hormones participate in the metabolism of water and electrolytes, and are also important for producing energy, this is a clinically difficult condition that can initially occur its most serious

form—adrenal crisis. The patient is vitally endangered with a severe clinical picture of arterial hypotension, dehydration, abdominal pain, nausea, and vomiting. Addisonian crisisis not such a common condition, but it is linked with a high mortality rate, as much as 45% [18]. The most common causes of adrenal gland insufficiency are autoimmune disease, then tumor infiltrations, and infarctions or hemorrhages within the glands, and so on. When the disease develops gradually, it is very difficult to establish the correct diagnosis, because the symptoms and signs are general and nonspecific, including malaise, weakness, muscle pain, loss of body mass, or hyperpigmentation on the skin.

Primary adrenal insufficiency occurs as a result of disturbed function of the adrenal gland itself, primarily in an autoimmune disease, severe infection, or cessation of the cortisol production in newborns due to congenital adrenal hyperplasia. Secondary adrenal insufficiency occurs due to dysfunction of the hypothalamus-pituitary-adrenal axis. Inadequate stimulation of the adrenal cortex occurs due to lack of adrenocorticotropic Hormone (ACTH). This condition frequently occurs associated with tumors of the pituitary gland, surgical interventions in that anatomical region, as well as after its radiation [19]. It is very important for clinicians to clarify whether a primary or a secondary adrenal insufficiency is present, because in the primary adrenal insufficiency, all the hormones produced by the adrenal cortex are absent while in the secondary insufficiency, only the hormones secreted under control of ACTH (cortisol and sex hormones). Substitution of aldosterone, which is controlled by the renin-angitensin system, is not required.

Addisonian crisis can also occur in people with adrenal insufficiency being on substitution therapy with glucocorticoids but experiencing specific circumstances, such as trauma, infection, increased effort, pregnancy, surgical interventions, and so on. It has to be underlined that the Addisonian crisis is an urgent endocrinological condition, where the prompt diagnosis and initiation of therapy is of crucial importance, since if the adequate therapy would not be started on time, a fatal outcome can occur.

Initial treatment in Addisonian crisis involves intravascular volume replacement with the crystalloid isotonic solutions and the correction of hypoglycemia by using 5% glucose solution. A correction of hormonal status by using glucocorticoids and mineralcorticoids is required, as well. Thus, in an adrenal crisis, it is necessary to immediately prescribe 100 mg intravenous hydrocortisone and then to continue with 50–100 mg intravenously every 6 hours during 1 day. In children, the recommended dose is 50 mg/m^2, with maximum of 100 mg. Given that quoted doses of glucocorticoids have minimal mineralocorticoid effects, it is not necessary additionally to prescribe fludrocortisone (a mineralcorticoid) at this time.

There are still challenges existing in treating Addisonian crisis. First of all, there are no adequate biomarkers that would show us the exact levels of cortisol in the tissues. It is encouraging that there are some studies that may provide us with a certain precision in determination of cortisol in hair, saliva, and subcutaneous fat tissue [20]. It is very difficult to prescribe quite precise individual effective dose, because the levels of glucocorticoids in the blood are under different influences, and of course, there is also an existing receptor polymorphism, which needs to be considered. It is also challenging to establish how much it is necessary to increase the initial doses of glucocorticoids during the treatment that are given as a substitution in a different setting of stress reactions. Although there are studies that could investigate this problem in clear situations of infections, surgical interventions, and trauma, it is quite another thing to determine how much glucocorticoids we need during an emotional stress. Therefore, more studies are needed to help us in determining a precise individual therapeutic regimen for Addisonian crisis.

7. Sepsis

Sepsis is a life-threatening condition accompanied with organic dysfunction, which is caused by an inadequate response of the body to an infection. Considering the high incidence and mortality, as well as long-term treatment in intensive care units associated with high costs, the sepsis has become a global problem in the recent decades. For these reasons, the scientific community has been working for a long time to develop common guidelines for the prevention, rapid detection, and treatment of sepsis through the Surviving Sepsis Campaign guide. The last recommendations were revised in 2021. The guidelines help in faster recognition of sepsis, earlier initiation of antibiotic therapy, and maintenance of the patient's hemodynamic status, respiratory support, and additional therapy.

Patients with sepsis have an increased heart and respiratory rate, decreased systolic pressure, disturbed consciousness, and elevated body temperature. Septic shock can occur very quickly, represented by circulatory, cellular, and metabolic instability, and it arise with a mean arterial pressure (MAP) of less than 65 mmHg and a lactate level of more than 2 mmol/L [21]. For that reason, it is of crucial importance regarding the sepsis therapy to establish hemodynamic stability and a tissue perfusion as soon as possible. There are clear guidelines for the amount and type of infusion solutions, as well as for prescribing vasopressors. The recommendations for the treatment of sepsis from 2016 advised the use of hydrocortisone intravenously only in patients who cannot reach hemodynamic stability despite fluid replacement therapy and the inclusion of the recommended vasopressor drugs.

The latest recommendations from 2021 state that intravenous hydrocortisone should be included for all patients being in septic shock and required vasopressor support. Hence, hydrocortisone is to be prescribed in a dose of 200 mg intravenously daily, 50 mg every 6 hours, or in a continuous infusion. Since the previous guidelines were instituted, three large studies have been published on the use of corticosteroids in the treatment of sepsis [22, 23]. Rigard et al. [24] also showed in their meta-analysis that systemic corticosteroids accelerated recovery from shock and shortened the time of vasopressor use. However, in this analysis, it was established that corticosteroids increase neuromuscular weakness, and there is still no clear connection between their use and the impact on mortality, too. So, taking all together previous facts into account, in an attempt to balance the pros and cons, these drugs are still to be included in the recommendations for the treatment of sepsis.

Given that the pathogenesis of sepsis is based on an inadequate immune response, it is logical that clinicians have long been trying to include corticosteroids as drugs with anti-inflammatory effects in the regular therapy. Liang et al. [25] showed in their meta-analysis that corticosteroids had no effect on mortality after 28 days or on long-term mortality, but they did detect some reduction in in-hospital mortality. They also showed that corticosteroids prolong time the patient is without vasopressor and ventilatory support as well as increase the incidence of side effects, such as hyperglycemia and hypernatremia. Moreover, the use of corticosteroids was associated with a shorter duration of hospitalization in the covered randomized studies. Nevertheless, the proper timing of systemic corticosteroids use in sepsis is still under investigation. This all lead us to the conclusion that more studies are needed to help clarifying the individual steps in the pathophysiological process of sepsis so that clinicians could decide on the type of therapy and the precise timing for each individual drug.

8. COVID-19

At the end of 2019, a number of patients with pneumonia of unknown etiology appeared in the Chinese city of Wuhan. It was quickly established that the causative agent of coronavirus disease (COVID-19) is a virus from the Coronaviridae family, which was named Novel Coronavirus, that is, SARS-Cov-2 (Severe Acute Respiratory Coronavirus). The disease has been proved to be extremely contagious; it quickly took the form of an epidemic, so afterward, on March 11, 2020, the World Health Organization (WHO) announced the beginning of a pandemic. Quick diagnosis was difficult due to the non-specificity of symptoms and laboratory findings. The therapy included antiviral drugs, anticoagulants, corticosteroids, biological and multivitamin therapy, as well as oxygen support.

At the beginning of the pandemic, the use of corticosteroids in the treatment of COVID-19 had a controversial character. Given that it was discovered early that the disease leads to impairment in regulation of the immune response and excessive production of cytokines, it was logical that drugs with an anti-inflammatory and immunosuppressive effects would have a therapeutic effect. It has been later shown that corticosteroids were useful in patients who were on oxygen support, especially those on mechanical ventilation, and these drugs should be avoided in those with a milder form of the disease or with specific comorbidities, due to a series of possible drug-induced unwanted effects [26].

Many randomized studies have shown that corticosteroids reduced mortality in COVID-19 [27]. This led the WHO to include corticosteroids in the guidelines for the treatment of patients with a severe form of the disease [28]. Accordingly, corticosteroids have also been shown to reduce mortality and the duration of mechanical ventilation in affected patients [29].

The large randomized study RECOVERY [30] investigated the effectiveness of dexamethasone administration in patients with COVID-19. The results showed that mortality in those who received dexamethasone was significantly lower compared to the group that received the other proposed therapy, especially in patients who were on mechanical ventilation or had an oxygen support. The mortality in those who did not require oxygen support did not differ from patients who were without corticosteroids. Also, the study showed that in those who did not take corticosteroids and were on oxygen support, deterioration in terms of the need for mechanical ventilation occurred more often.

The WHO provided a prospective meta-analysis of existing research on the treatment of COVID-19, the so-called REACT study [31]. The analysis showed that mortality was lower in the groups of patients who received corticosteroids. Mortality did not differ between the dexamethasone and the hydrocortisone groups. There was no difference to in terms of the amount of dose, as well. This meta-analysis showed that the success of therapy depended on the severity of the clinical presentation. Namely, the efficacy of the corticosteroids use was more pronounced in the group that presented severe clinical features with the need for oxygen support or mechanical ventilation. This meta-analysis also showed the effect of corticosteroids on prolonging the elimination of the virus through the mucous membranes of the nasopharynx and oropharynx. This resulted in prolonging the time of the positive result of the PCR test and was explained by the suppression of the immune response. Based on the previous facts, the WHO made adjusted recommendations for the treatment of COVID-19 infection and included corticosteroids in standard therapy. The European Respiratory Society gave a strong recommendation for the systemic use of corticosteroids, as well [32].

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Author details

Miroslav Radenković[1*] and Ivana Milićević[2]

1 Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

2 Department of Emergency Medicine, Emergency Center Belgrade, University Clinical Center of Serbia, Belgrade, Serbia

*Address all correspondence to: miroslav.radenkovic@med.bg.ac.rs

References

[1] Ramamoorthy S, Cidlowski JA. Corticosteroids–Mechanisms of action in health and disease. Rheumatic Diseases Clinics of North America. 2016;**42**(1):15-31

[2] Mirijello A, Tosoni A. On behalf of the internal medicine sepsis study group. New strategies for treatment of sepsis. Medicina (Kaunas, Lithuania). 2020;**56**(10):E527

[3] Heron M. Deaths: Leading causes for 2017. National Vital Statistics Reports. 2019;**68**(6):1-77

[4] World Health Organization. The top 10 causes of death. 2018

[5] Leuppi JD, Shuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease. Journal of the American Medical Association. 2013;**309**(21):2223-2231

[6] Wedzicha JA, Miravittles M, Hurst JR, et al. Management of COPD exacerbations: European Respiratory Society guidline. The European Respiratory Journal. 2017;**49**:1600791

[7] Nakamura Y, Tamaoki J, Nagase H, Yamaguchi M, et al. Japanese Society of Allergology. Japanese guidelines for adult asthma. 2020. Allergology International. 2020;**69**(4):519-548

[8] Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: The GOLD science committee report 2019. European Respiratory Journal. 2019;**53**(5):1900164. DOI: 10.1183/13993003.00164-2019

[9] Fuhlbrigge A, Peden D, Apter AJ, Boushey HA, Camargo CA Jr, Germ J, et al. Asthma outcomes: Exacerbations. The Journal of Allergy and Clinical Immunology. 2012;**129**:s34-s48

[10] Global Initiative for Asthma Management and Prevention (GINA) Difficult –to-Treat and Severe Asthma in Adolescent and Adult Patients, Diagnosis and Management. 2019. Available from: www.ginasthma.org

[11] Price D, Castro M, et al. Short-course systematic corticosteroids in asthma: Striking balance between efficancy and safety. European Respiratory Review. 2020;**29**(155):190151

[12] Vorham J, Menzies Gow A, Tran TN, et al. Longitudinal systemic corticosteroid utilisation for asthma and other disease in the United Kngdom from 1990 to 2018: A population based cohort analysis. Thorax. 2021;**76**(supl. 1):A21

[13] Chakraborty RK, Basnet S. Status Asthmaticus. 2022 Oct 10. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022

[14] Nagata S, Ohbe H, Matsui H, Fushimi K, Yasunaga H. Glucocorticoids and rates of biphasic reactions in patients with adrenaline treated anaphylaxis: A propensity score matching analysis. International Archives of Allergy and Immunology. 2022;**183**(9):939-945

[15] Whyte AF, Soar J, Dodd A, Hughes A, Sargant N, Turner PJ. Emergency treatment of anaphylaxis; concise clinical guidance. Clinical Medicine (London, England). 2022;**22**(4):332-339

[16] Liu Z, Yang Y, He L, Pang M, Luo C, Liu B, et al. High-dose

methylprednisolone for acute traumatic spinal cord injury: A meta-analysis. Neurology. 2019;**93**(9):e841-e850

[17] Nelson CM, Lennon VA, Lee H, Krug RG 2nd, Kamalova A, Madigan NN, et al. Glucocorticoids target ependymal glia and inhibit repair of the injured spinal cord. Frontiers in Cell and Developmental Biology. 2019;**7**:56

[18] Betterle C, Pressoto F, Furmaniak J. Epidemiology, pathogenesis and diagnosis of Addison s disease in adults. Journal of Endocrinological Investigation. 2019;**42**(12):1407-1433

[19] Dineen R, Thompson CJ, Sherlock M. Adrenal crisis: Prevention and management in adult patients. Therapeutic Advances in Endocrinology and Metabolism. 2019;**10**:2042018819848218

[20] Claessen KM, Andela CD, Biermasz NR, Pereira AM. Clinical unmet needs in the treatment of adrenal crisis: Importance of the patient's perspective. Frontiers in Endocrinology. 2021;**12**:701365

[21] Huang M, Cai S, Su J. The pathogenesis of sepsis and potential therapeutic targets. International Journal of Molecular Sciences. 2019;**20**(21):5376

[22] Annane D, Renault A, Brun-Buisson C, et al. CRICS-TRIGGERSEP network. Hydrocortisone plus fludrocortisone for adults with septic shock. The New England Journal of Medicine. 2018;**378**:809-818

[23] Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. The New England Journal of Medicine. 2018;**378**:797-808

[24] Rygard SL, Butler E, Granholm A, et al. Low-dose corticosteroids for adult patients with septic shock: A systematic review with meta-analysis and trial sequential analysis. Intensive Care Medicine. 2018;**44**:1003-1016

[25] Liang H, Song H, Zhai R, Song G, Li H, Ding X, et al. Corticosteroids for treating sepsis in adult patients: A systematic review and meta-analysis. Frontiers in Immunology. 2021;**12**:709155

[26] Milenkovic M, Dukic M, Brajkovic M, Klasnja S, Toskovic B, Zdravkovic M. Primenakortikosteroida u terapiji COVID -19 infekcije. Serbian Journal of Anesthesia and Intensive Therapy. 2021;**43**(5-6):85-96

[27] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, JAC S, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. The Journal of the American Medical Association. 2020

[28] Lamontagne F, Agarwal A, Rochwerg B, Siemieniuk RA, Agoritsas T, Askie L, et al. A living WHO guideline on drugs for COVID-19. BMJ. 2020;**370**:m3379

[29] Chadhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID 19 ARDS: A systematic review and meta-analysis. Intensive Care Medicine. 2021;**47**(5):521-537

[30] Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. On behalf of the RECOVERY collaborative group. Dexamethasone in hospitalized patients with COVID-19. The New England Journal of Medicine. 2021;**384**(8):693-704

[31] The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) working Group. Association

between administration of systemic corticosteroids and mortality among critically Ill patients With COVID-19: A meta-analysis. The Journal of the American Medical Association. 2020;**324**(13):1330-1341

[32] Agoristas T, John Adabie Appiah J, Arabi Y, Blumberg L, Calfee C, Cao B, et al. Corticosteroids for COVID-19-Living guidance (World Health Organization). 2020. Available from: https://apps.who.int/iris/handle/