DOI: 10.20514/2226-6704-2022-12-1-22-34 УДК 616.72-002.77-089-06-085.276

В.В. Лялина*[1], С.В. Борисовская[1,2], Э.А. Скрипниченко[1], О.А. Эттингер[1,2], Т.М. Паджева[3], И.Г. Никитин[1,4]

[1] — Кафедра госпитальной терапии № 2 ЛФ ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, Москва, Россия
[2] — ГБУЗ «ГКБ имени В.М. Буянова ДЗМ», Москва, Россия
[3] — ГБУЗ «ГКБ № 40 ДЗМ», Москва, Россия
[4] — ФГАУ «НМИЦ «ЛРЦ» Минздрава России, Москва, Россия

ПЕРИОПЕРАЦИОННОЕ ВЕДЕНИЕ ПАЦИЕНТОВ С РЕВМАТОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ: РЕКОМЕНДАЦИИ ПО ПРИМЕНЕНИЮ ГЛЮКОКОРТИКОСТЕРОИДОВ, БОЛЕЗНЬ-МОДИФИЦИРУЮЩИХ АНТИРЕВМАТИЧЕСКИХ ПРЕПАРАТОВ, ГЕННО-ИНЖЕНЕРНЫХ БИОЛОГИЧЕСКИХ ПРЕПАРАТОВ, НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ ПРЕПАРАТОВ

V.V. Lyalina*[1], S.V. Borisovskaya[1,2], E.A. Skripnichenko[1], O.A. Ettinger[1,2], T.M. Padzheva[3], I.G. Nikitin[1,4]

[1] — Pirogov Russian National Research Medical University (Pirogov Medical University), Moscow, Russia
[2] Buyanov City Clinical Hospital, Moscow, Russia
[3] Moscow City Clinical Hospital № 40, Moscow, Russia
[4] National Medical Research Center of Treatment and Rehabilitation, Moscow

Perioperative Management of Patients with Rheumatic Diseases: DMARDs, Biological Agents, Steroids, and NSAIDs

Резюме

Пациенты с ревматологическими заболеваниями характеризуются рядом особенностей, которые необходимо учитывать в процессе периоперационного ведения. В частности, ревматологические заболевания приводят к двигательным ограничениям, нарушению структуры и снижению функции многих органов и систем, необходимости постоянного приёма иммуносупрессивных и других лекарственных средств. В связи с этим у пациентов отмечается повышенный риск разнообразных интраоперационных и послеоперационных осложнений.

*Контакты: Вера Валерьевна Лялина, e-mail: vera_lyalina@mail.ru
*Contacts: Vera V. Lyalina, e-mail: vera_lyalina@mail.ru
ORCID ID: https://orcid.org/0000-0002-4262-4060

Целью данной публикации является рассмотрение современных рекомендаций по периоперационному ведению пациентов с ревматологическими заболеваниями. В данной публикации рассматривается один из наиболее сложных вопросов — периоперационное применение лекарственных препаратов: глюкокортикостероидов, базисных болезнь-модифицирующих антиревматических препаратов, генно-инженерных биологических препаратов и нестероидных противовоспалительных препаратов.

Ключевые слова: *ревматоидный артрит, периоперационное ведение, базисные болезнь-модифицирующие антиревматические препараты, БМАРП, метотрексат, генно-инженерные биологические препараты, системная красная волчанка, глюкокортикостероиды, ГКС*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 27.04.2021 г.

Принята к публикации 01.09.2021 г.

Для цитирования: Лялина В.В., Борисовская С.В., Скрипниченко Э.А. и др. ПЕРИОПЕРАЦИОННОЕ ВЕДЕНИЕ ПАЦИЕНТОВ С РЕВМАТОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ: РЕКОМЕНДАЦИИ ПО ПРИМЕНЕНИЮ ГЛЮКОКОРТИКОСТЕРОИДОВ, БОЛЕЗНЬ-МОДИФИЦИРУЮЩИХ АНТИРЕВМАТИЧЕСКИХ ПРЕПАРАТОВ, ГЕННО-ИНЖЕНЕРНЫХ БИОЛОГИЧЕСКИХ ПРЕПАРАТОВ, НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ ПРЕПАРАТОВ. Архивъ внутренней медицины. 2022; 12(1): 22-34. DOI: 10.20514/2226-6704-2022-12-1-22-34

Abstract

The rheumatic patients are characterized by various structural and functional changes, caused by chronic disease, the necessity of constant medication intake, including anti-inflammatory drugs and immunosuppressants. In this regard, the rheumatic patients have an increased risk of intraoperative and postoperative complications. The purpose of this publication is to review current recommendations on the topic of perioperative management of rheumatic patients. The publication consists of two parts. In the first part we review the issues of perioperative administration of disease-modifying antirheumatic drugs, biologics, steroids, and nonsteroidal anti-inflammatory drugs.

Key words: *rheumatoid arthritis, perioperative management, perioperative care, disease-modifying anti-rheumatic drug, methotrexate, biological agents, systemic lupus erythematosus, glucocorticoids, surgical intervention, NSAIDs*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 27.04.2021

Accepted for publication on 01.09.2021

For citation: Lyalina V.V., Borisovskaya S.V., Skripnichenko E.A. et al. Perioperative Management of Patients with Rheumatic Diseases: Glucocorticoids, DMARDs, Biological Agents and NSAIDs. The Russian Archives of Internal Medicine. 2021; 11(5): 22-34. DOI: 10.20514/2226-6704-2022-12-1-22-34

AAHKS — American Association of Hip and Knee Surgeons, ACR — American College of Rheumatology, ACTH — adrenocorticotropic hormone, AI — adrenal insufficiency, COX — cyclooxygenase, DMARDs — disease modifying anti-rheumatic drugs, GC activity — glucocorticoid potency of steroids, HPAA — hypothalamic-pituitary-adrenal axis, IRD — inflammatory rheumatic diseases, IV — intravenous, MC activity — mineralocorticoid potency of steroids, NSAIDs — non-steroid anti-inflammatory drugs, OR — operating room, PDE-4 — phosphodiesterase-4, PO — peroral, RD — rheumatic diseases, SLE — systemic lupus erythematosus, SQ — subcutaneous, TNF — tumor necrosis factor, WBC — white blood cells, WHO — world health organisation

Introduction

Rheumatic Diseases (RD) are characterized by chronic course and systemic involvement, leading to significant structural alterations and functional deficiency in many organs. The treatment of RD includes long-term use of various anti-inflammatory agents and immunosuppressants such as non-steroidal anti-inflammatory drugs (NSAIDs), steroids, disease-modifying anti-rheumatic drugs (DMARDs) and biological agents. Both the impact of the disease itself and the adverse effects of medications result in an increased risk of infectious and cardiovascular complications in rheumatic patients. This has to be considered perioperatively.

Well before the elective surgery, the RD patients should be carefully assessed by rheumatologist in regard to the disease activity and organ involvement, which may affect the course of the surgical procedure and postoperative recovery. It is recommended to schedule the operation for the period of remission or minimal activity of the disease. If necessary, the doses of constant medications should be adjusted. Cardiovascular and thrombo-

Table 1. *Guideline for the perioperative use of antirheumatic drugs [1]*

DMARDs: CONTINUE these medications through	**Dosing interval**	**Continue/withhold**
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide	Daily	Continue
Doxycycline	Daily	Continue
BIOLOGIC AGENTS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence of wound healing problems, surgical site infection, or systemic infection.	**Dosing interval**	**Schedule Surgery (relative to last biologic agent dose administered) during**
Adalimumab	Weekly or every 2 weeks	Week 2 or 3
Etanercept	Weekly or twice weekly	Week 2
Golimumab	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Infliximab	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Abatacept	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Certolizumab	Every 2 or 4 weeks	Week 3 or 5
Rituximab	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab	Every week (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra	Daily	Day 2
Secukinumab	Every 4 weeks	Week 5
Ustekinumab	Every 12 weeks	Week 13
Belimumab	Every 4 weeks	Week 5
Tofacitinib: STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period.	**Dosing interval**	**Continue/withhold**
Mycophenolate mofetil	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue
Tacrolimus	Twice daily (IV and PO)	Continue
NOT-SEVERE SLE: DISCONTINUE these medications 1 week prior to surgery	**Dosing interval**	**Continue/withhold**
Mycophenolate mofetil	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Withhold

embolic risk management as well as infectious complications prevention in RD patients are implemented within the framework of generally accepted guidelines. Besides, there are special recommendations for certain types of operations and certain diseases.

In case of an emergency operation, the perioperative management should be considered individually on the basis of available guidelines.

The literature review consists of two parts. This part highlights the issues of perioperative use of DMARDs, biologics, steroids and NSAIDs.

DMARDs and biologics

The most detailed information on perioperative use of DMARDs is presented in the guidelines of the American College of Rheumatology [1]. The summary is given in Table 1 and illustrated by schemes 1 and 2. The guidelines relate to the knee and hip joint replacement surgery in patients with rheumatoid arthritis, seronegative spondyloarthritis and systemic lupus erythematosus (SLE) and thus may well be extrapolated to other major operations in RD patients.

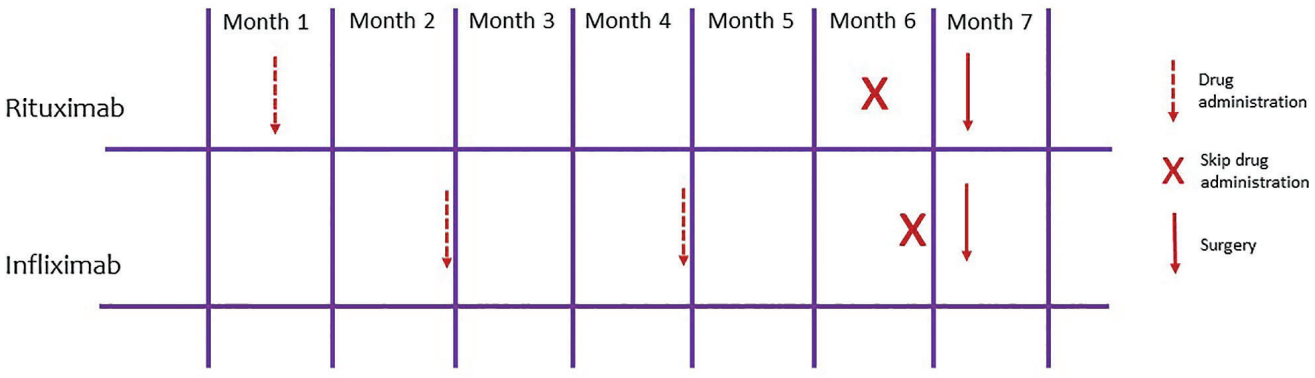
Following from Table 1, it is not required to withdraw the DMARDs perioperatively. In the case of mild SLE however, it is recommended to stop DMARDs a week before surgery.

The administration of biologics should be discontinued prior to the surgery and the procedure should be scheduled for the end of the dosing cycle of a particular drug [2]. This recommendation is internationally agreed on [3]. The temporary withdrawal of the biologics aims to reduce the risk of infectious complications [4, 5], as the avoidance of postoperative infection is more important for the RD patients than the potential exacerbation of their disease [1]. In addition, it is known that 5 half-life periods are necessary for the complete elimination of the drugs [3]. Given the comparatively short period of perioperative pausing, the risk of exacerbation is very low.

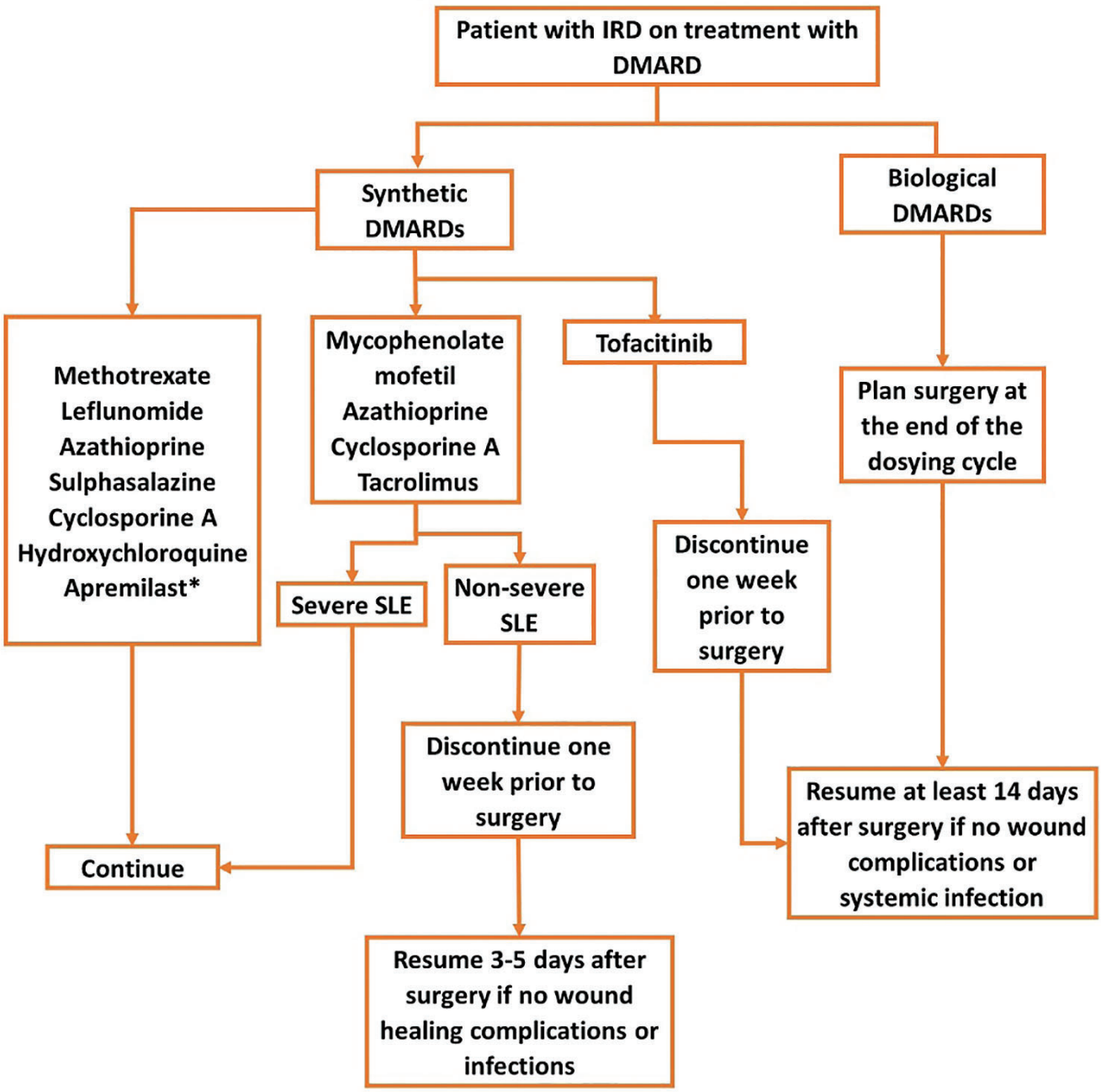
The timing of preoperative withdrawal of biologics is based on the cycle of their dosing, rather than their half-life period. This is justified by the fact that the half-life period of biologics may not correspond to the duration of their immunosuppressive effect. Moreover, the duration has not been established for some of them. In this regard, the dosing cycle was chosen as a more reliable criterion for determining the pausing interval [1].

The perioperative dosing of biologics is illustrated in Scheme 1 by the examples of rituximab and infliximab. In patients receiving rituximab every 6 months, the surgery has to be scheduled on the week following the missed dose (i.e., the second week of the seventh month, or during the seventh month). In patients receiving infliximab every 8 weeks the operation has to be scheduled on the 9th week after the last injection. In case of adalimumab — on the 3rd week and belimumab — on the 5th week. [1]

Resuming the normal medication after the surgery is recommended in the healing stage of the wound (which usually occurs 14 days after surgery) and in the absence of any signs of infection and inflammation of the wound. Besides, the renal and hepatic functions should be sufficient [1]. Resuming the treatment in RD patients should be considered individually, based off the condition of the wound and the general condition of the patient.



Scheme 1. *Biological agents withdrawal on the example of rituximab and infliximab (author's illustration)*



Scheme 2. *The use of DMARDs in the perioperative period [2]*

Note: IRD — Inflammatory rheumatic diseases
DMARD — disease-modifying anti-rheumatic drugs
SLE — systemic lupus erythematosus
*No evidence, in high-risk patients suspend 3 days before surgery

In addition to the general guidelines on the resumption of the drugs, there are particular recommendations for some biologics. For tumor necrosis factor (TNF) inhibitors and rituximab the recommended time of resumption is 4 weeks after surgery, while tocilizumab can be continued immediately after surgery, provided that the wound healing process is normal and there are no infections [3].

Currently, there are no guidelines for the perioperative administration of apremilast (a PDE-4 inhibitor), which is used for the treatment of psoriatic arthritis. There is evidence that this is a generally safe drug characterized by the low risk of infectious complications. In high risk patients however, apremilast may be discontinued 3 days before surgery, based on its half-life period [2].

There are some specific recommendations for perioperative management in SLE (see Scheme 2).

According to American College of Rheumatology/ American Association of Hip and Knee Surgeons (ACR/ AAHKS) guidelines, the patients with severe and non-severe forms of SLE should be distinguished [2].

The severe SLE implies that the patient has the most severe involvement of the organs such as the skin syndrome, central nervous system involvement, hemolytic anemia, thrombocytopenia, vasculitis (except for mild cutaneous vasculitis), myocarditis, pneumonitis, myositis (including oculomotor muscle myositis), enteropathy, lupus pancreatitis, cholecystitis or hepatitis, severe keratitis, posterior severe uveitis/retinal vasculitis and optic neuritis [6].

In patients with severe SLE it is recommended to continue the normal dose of methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus perioperatively, since the risk of exacerbation exceeds the risk of infectious complications. The ACR/AAHKS group also recognizes however the importance of making decisions on a case-by-case basis.

In mild SLE, it is recommended to stop the normal dose of mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus treatments 1 week before surgery in order to restore the immune response. These drugs should be resumed 3-5 days after the operation, provided that the wound healing process is normal and there are no infections. [1]

Steroids

1. *General information*

The basic secretion of adrenal glands is equivalent to 20-30 mg of cortisol a day (5-7.5 mg of prednisone). With high level stress, such as major surgery under general anesthesia, this amount increases tenfold, up to 200-300 mg of cortisol (50-75 mg of prednisone). Usually, the peak of cortisol levels is observed within 24 hours after surgery and returns to normal after 72 hours [9].

Steroid intake can affect the normal function of the hypothalamic-pituitary-adrenal system and suppress the endogenous production of cortisol. This can result in adrenal insufficiency (AI) which means a lack of cortisol secretion under stress and the inability to adequately maintain physiological functions, such as vascular tone and blood pressure. The risk of AI justifies the supraphysiological dosing of steroids in the perioperative period (aka stress dosing). The use of 300 mg of hydrocortisone daily for several days has become a common perioperative practice for patients receiving steroid therapy [7].

The contemporary understanding however states that the perioperative dosage of steroids should be considered on a case-by-case basis. The decision should be based on steroid intake history, hypothalamic- pituitary-adrenal axis (HPAA) function, as well as the type and duration of the surgery. In addition, it is necessary to take into account whether etomidate will be used for anesthesia (currently not registered in Russia) [7].

2. *Assessment of the patient's steroid status*

Based off the history of steroid intake the patients are viewed in three distinctive categories. The first group includes the patients with low risk of HPAA suppression and AI. The second group is characterized by the high risk of AI. The third group involves the patients with intermediate risk and several special subgroups.

Group 1. Low risk of AI; suppression of HPAA is not expected in the following cases [7]:

- **a.** Intake of any dose of steroids in the past for less than three weeks
- **b.** Morning intake of less than 5 mg a day of prednisone or its equivalent for any period of time in the past
- **c.** Current intake of less than 10 mg of prednisone or its equivalent every other day.

The patients of the low-risk group do not require any additional administration of steroids perioperatively. This means that they either do not need steroids at all (as for 1a and 1b), or they should continue taking

Table 2. *Perioperative use of stress doses of glucocorticoids [9]*

Level of surgical Stress	Surgical procedure	Stress-dose steroids
Superficial procedure	Skin biopsy	Continue daily dose of corticosteroids.
Minor	· Procedures under local anesthesia and <1 hour; · colonoscopy; · cataract surgery; · carpal tunnel release; · tenosynovectomy; · knee arthroscopy; · most minor podiatry/orthopedic foot procedures (hammer toe correction, toe fusion).	Continue daily dose of corticosteroids Hydrocortisone on call to OR for urgent use if necessary.
Moderate	· unilateral total joint replacement; · complex foot reconstruction; · lower extremity vascular surgery; · uncomplicated appendectomy; · gallbladder removal.	Hydrocortisone 50–100 mg IV intraoperatively in OR, then 50 mg IV every 8 hours for 24 hours. On the second postoperative day, hydrocortisone may be tapered over an additional 24 hours or preoperative daily oral dosing may be resumed.
Major	· multiple trauma; · colon resection; · bilateral joint replacement; · revision arthroplasty; · multiple level spinal fusion; · any surgery requiring cardiopulmonary bypass.	Hydrocortisone 100 mg IV intraoperatively in OR, then 100 mg IV every 8 hours for 24 hours, then 50 mg IV every 8 hours for the next 24 hours, then resume the preoperative daily dose on third postoperative day.

Note: OR — operating room, IV — intravenous

Table 3. *Comparative activity of glucocorticoids for systemic administration*

Steroids	Equivalent doses (mg)	GC* potency	MC** potency	Half-life	
				serum (minutes)	tissue (days)
Short-acting (8–12 hours):					
Hydrocortisone	20	1	1	90	0,5
Cortisone	25	0,8	1	30	0,5
Intermediate-acting (12–36 hours):					
Prednisolone	5	4	0,8	200	0,5-1,5
Prednisone	5	4	0,8	60	0,5-1,5
Methylprednisolone	4	5	0,5	200	0,5-1,5
Long-acting (36–72 hours):					
Triamcinolone	4	5	-	> 200	1-2
Dexamethasone	0,75	30	-	> 300	1,5-3
Betamethasone	0,75	30	-	> 300	1,5-3

Note: *GC activity — glucocorticoid potency of steroids, **MC activity — mineralocorticoid potency of steroids

their usual dose. The HPAA function test is not advised in these patients, since it does not predict the development of AI after surgery [8]. During the operation, the low-risk patients require standard hemodynamic monitoring.

Group 2. High risk of AI; suppression of the HPAA function is assumed in the following cases:

a. Current intake of prednisolone is 20 mg daily (or equivalent) for more than three weeks

b. Current steroid intake accompanied by Cushing's syndrome.

Patients with high risk require additional doses of steroids perioperatively in accordance with the type of operation (Table 2):

Besides the low and high-risk groups, there are also special categories of patients with a history of steroid intake.

Group 3. Special groups of patients with a history of steroids intake

a. Patients in whom it is impossible to judge the HPAA function confidently (so called "intermediate risk") [7]:

In patients who have been taking 5 to 20 mg/day of prednisone (or equivalent) for more than three weeks, the HPAA function varies significantly. This variability is possibly related to differences in the metabolising rate of steroids.

In addition, doses lower than the equivalent of 5 mg/day of prednisone taken in the evening can disrupt normal daily fluctuations of steroids and distort the patient's response to surgical stress [10].

It is recommended to assess the HPAA in the patients of the "intermediate group" (See "Assessment of the HPAA")

b. Patients who stopped taking steroids less than a year before surgery

The full recovery of HPAA takes one year. In this regard, the perioperative steroid administration in these patients should be based off the same rules as for the high, low and intermediate groups.

c. Patients who receive inhaled or topical steroids

Long-term use of inhaled or topical steroids can potentially cause suppression of HPAA, although it rarely results in AI [11]. The degree of HPAA suppression depends on the class of activity, dose, duration, frequency and time of administration of steroids.

It is recommended to evaluate the adrenal function preoperatively in patients with the following history:

- ≥ 750 mcg/day of fluticasone (≥1500 mcg/day for other inhaled steroids) for more than three weeks before surgery;
- ≥ 2 g/day of topical steroids with high or ultra-high activity (classes I-III) for more than three weeks before surgery (Table 4);

In addition, the HPAA should be evaluated in all the patients with Cushing's syndrome or any symptoms of AI [12].

d. Patients who received intra-articular or spinal injections of steroids.

The HPAA suppression has been described following intra-articular as well as spinal injections of steroids since the certain amount of the medication enters the bloodstream [13-15]. It is known that the degree of suppression depends on the dose, the interval between and the number of steroid injections, but is also possible with a single administration of a small dose.

The risk of perioperative AI in patients of this group is considered relatively low, however it is recommended to assess the HPAA function in those who received three or more intra-articular or spinal steroid injections within three months before surgery [14], as well as in the case of Cushing's syndrome [16].

Table 4. *Classification of local glucocorticoids by potential activity (according to WHO)*

Ultra-high potency topical corticosteroids (class I) — clobetasol propionate cream (0.05 %) and others;
High potency topical corticosteroids (classes II-III) — betamethasone valerate ointment (0.1 %), betamethasone dipropionate ointment or cream (0.05 %), triamcinolone acetonide ointment (0.1 %) and others;
Moderate potency topical corticosteroids (classes IV-V) — hydrocortisone valerate ointment 0.2 %, triamcinolone acetonide cream 0.1 %, betamethasone dipropionate lotion 0.02 %, betamethasone valerate cream 0.1 %, fluocinonide acetonide cream 0.025 %, hydrocortisone butyrate cream 0.1 %, hydrocortisone valerate cream 0.2 %, triamcinolone acetonide lotion 0.1 % and others;
Low potency topical corticosteroids (classes VI-VII) — betamethasone valerate lotion 0.05 %, fluocinolone acetonide solution 0.01 %, hydrocortisone acetate cream (1 %), methylprednisolone acetate cream 0.25 % and others.

3. *Evaluation of the HPAA function*

It is important that in case of urgent or emergent surgery no HPAA evaluation is necessary. All patients therefore who have a risk of perioperative AI require empirical additional doses of steroids.

The additional dosing is based off the type and expected duration of the operation and presented in Table 2.

4. *Evaluation of morning serum cortisol*

The evaluation of morning (before 8 am) serum cortisol is proposed as a screening method for assessing the probability of secondary AI [17, 18]. It is extremely unreliable however and is uninformative in steroid taking patients, so it is rarely used in clinical practice.

5. *ACTH Stimulation Tests*

A so — called "short" test implies the use of synacten which is an ACTH synthetic analog (currently not registered in Russia). The test can be carried out at any time of day regardless of meals. First, a blood sample is obtained to determine the initial level of cortisol. Then, a solution of synacten (250 mcg in 5 ml of saline) is injected intravenously, slowly, in the course of two minutes. After 30 minutes, a second blood sample is obtained and the cortisol level is measured.

The cortisol level >18 mcg/dl (497 nmol/l) in the second sample indicates a sufficient reserve of the adrenal glands, and additional doses are not required perioperatively [19, 20]. Patients with an insufficient adrenal reserve should receive additional doses (Table 2).

The ACTH stimulation test may be normal in patients with acute ACTH deficiency (for example, within 2-4 weeks after pituitary surgery). In this case the indicators of the HPAA function will be distorted [21]. In these patients, an insulin tolerance test or metyrapone stimulation can be performed to assess the HPAA. These tests however are difficult to perform in real clinical practice. Therefore, patients who have recently undergone pituitary surgery and have a risk of acute ACTH deficiency are recommended empirical additional doses of steroids.

6. *Application of etomidate*

Etomidate was previously widely used in anesthesia; however, it showed an inhibitory effect over the steroid synthesis, resulting in acute AI [22]. In this regard, etomidate should be avoided, especially in patients with a risk of adrenal suppression and AI. If etomidate is still used, the patients should receive steroids perioperatively and/or be carefully monitored for any clinical signs of AI [23].

In patients with possible suppression of the HPAA function, the presence of unexplained nausea, vomiting, hypotension, orthostatic hypotension, changes in mental status, hyponatremia or hyperkalemia require a random cortisol test. Regarding the urgency, empirical therapy with additional steroids may be required. It is important that the numerous postoperative stressors, such as infection, myocardial infarction, bleeding or other complications, may call for the introduction of additional steroids.

7. *Assessment of the type and duration of the operation.*

The most common schemes of perioperative steroid dosing the approximate doses are indicated in Table 2.

8. *Potential side effects of steroids in the perioperative period*

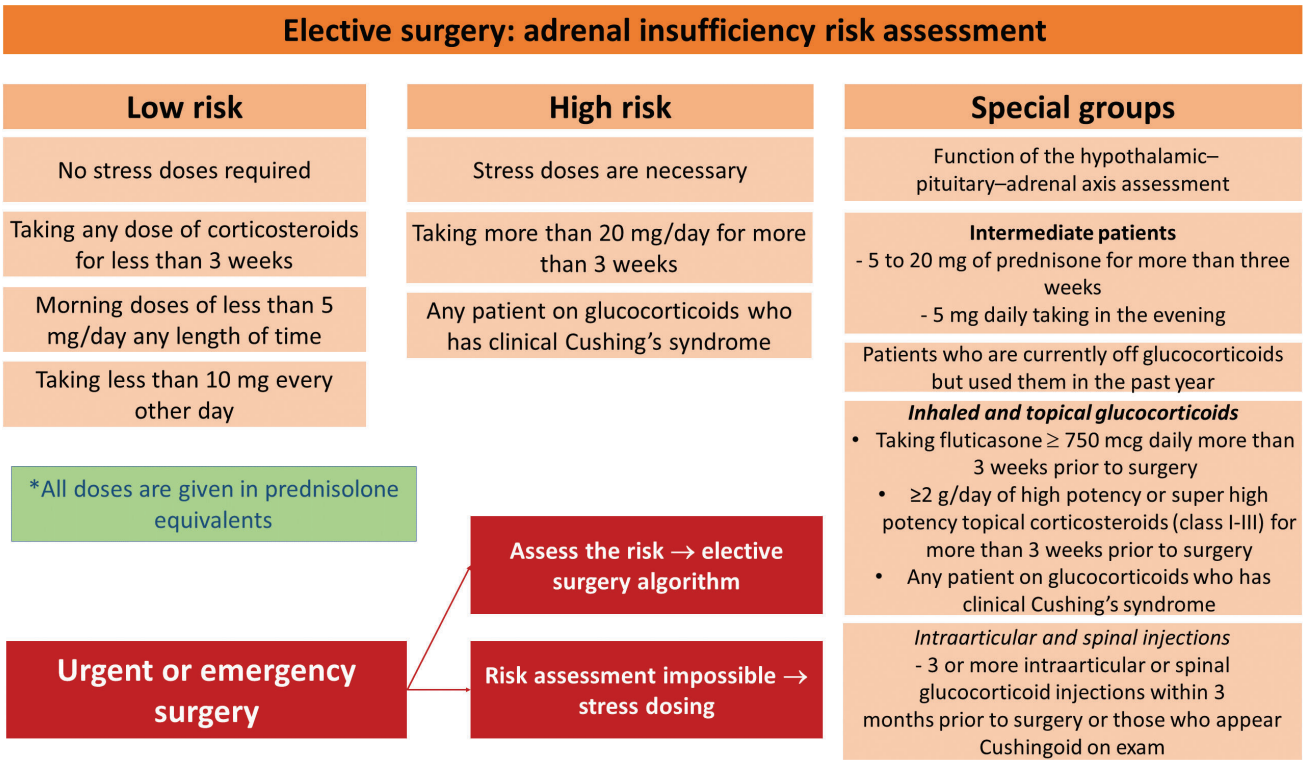
In addition to the increased risk of infectious complications and suppression of the HPAA function, there are some other potential adverse effects of steroids, affecting the results of surgical intervention [7]:

- poor wound healing;
- thinning of the skin, easy tissue injury, fragility of superficial blood vessels (for example, moderate pressure can cause a hematoma or ulceration of the skin, removing the patch can tear the skin, and sutures can tear the intestinal wall);
- increased risk of fractures, gastrointestinal bleeding or ulcers, hyperglycemia; arterial hypertension; fluid retention.

9. *The risk of infectious complications against the background of the use of steroids.*

In steroid taking patients a careful monitoring is required postoperatively for the timely detection of infectious complications. This includes the control of WBC, C-reactive protein and procalcitonin levels. It also shouldn't be omitted that steroids can suppress a febrile reaction.

In knee and hip replacement surgery, the "safe dose" in regard to the risk of infectious complications should not exceed 10 mg of prednisone a day [3] or 20mg a



Scheme 3. *Perioperative risk assessment of adrenal insufficiency*

day according to other sources [1]. This applies to patients who have been taking steroids for a long time. It remains unclear whether there is a "safe period" for short-term steroid use in the preoperative period. The data, although limited, shows the detection of immunosuppression after two weeks of 20 mg of prednisone a day [1].

Thus, to reduce the risk of infectious complications, it is advisable to adjust the dose of steroids to the 10 mg/day target. Dose adjustment should be started 3-6 months before the elective surgery [24].

In patients who cannot reduce the dose because of the risk of deterioration, it is especially important to ensure thorough sterility and treatment of the skin, tight covering and proper antibiotic prophylaxis [2].

A normal dose of steroids exceeding 10-20 mg/day is not only associated with the risk of infections, but also indicates high activity of the disease, which in itself carries a risk [3]. In patients undergoing high-dose steroid therapy, the elective surgery is recommended to be postponed until better control of the disease activity, allowing to reduce the dose of steroids. If the surgery is performed for emergency indications, it is necessary to provide enhanced prevention of infectious complications, as well as AI. [2]

Nonsteroidal anti-inflammatory drugs (NSAIDs)

It is recommended to cancel NSAIDs before surgery for a period of time amounting to 3-5 half-lives (Table 5) with the aim of platelet function recovery. Temporary withdrawal of NSAIDS allows to avoid the most common side effect of this class (an increased risk of bleeding; in particular, gastrointestinal bleeding as well as bleeding in the area of the surgical wound).

It is believed that celecoxib does not affect the function of platelets, thus assumed the safest NSAID in terms of the risk of bleeding [26].

At the same time, it is known that there is a poor correlation between the half-life and COX-1 inhibition and decrease in platelet function. In addition, the relationship between the duration of NSAIDs withdrawal and intra- and postoperative clinically significant bleeding is not clearly defined. It was found that for most NSAIDs, platelet function normalizes within three days after pausing, which suggests that NSAIDs should be discontinued at least three days before surgery. Ibuprofen can be discontinued 24 hours before surgery [27].

It is possible to resume taking NSAIDs 2-3 days after surgery, provided the patient's condition is stable [2].

Table 5. *The half-life of NSAIDs [24]*

NSAIDs	Half-life, h	Withdrawal time before surgery
Ibuprofen	1,6-1,9	10 hours
Naproxen	12-15	3 days
Diclofenac	2	10 hours
Indomethacin	4.5	1 days
Piroxicam	30	6 days
Etodolac	6-7	1,5 days
Nabumetone	24-29	6 days
Celecoxib	11	Withdrawal not required
Meloxicam	15-20	5 days

If the patient needs NSAIDs perioperatively and the risk of adverse effects is high, it is possible to switch from a medication with a long-lasting effect to the one with a shorter half-life (Table 5). At the same time, it is not recommended to use selective COX-2 inhibitors for the reasons of cardiovascular safety.

If pain relief is necessary and NSAIDs use is objectionable, it is recommended to consider paracetamol, tramadol or opioids as an alternative.

In addition, it is necessary to check with patients whether they take any medications and supplements on their own. Many supplements can affect platelet function, increasing the risk of bleeding or interact with anesthesia (such as ginkgo biloba, ginger, etc.) [9]

Conclusion

This article provides a review of current guidelines and recommendations for the perioperative administration of the main medications used in rheumatology. The dose adjustment for NSAIDs and steroids is recommended to be carried out in advance. It is not required to withdraw or adjust DMARDs in most cases, and there are special instructions for the perioperative use of biologics.

The perioperative management of infectious, thromboembolic and cardiovascular risks, as well as the impact of some special conditions characteristic to RD, will be reviewed in the second part of the publication.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Лялина В.В. (ORCID ID: https://orcid.org/0000-0002-4262-4060): концепция и дизайн статьи, редактирование текста, обзор публикаций по теме, взаимодействие авторов

Борисовская С.В. (ORCID ID: https://orcid.org/0000-0002-9365-1472): научная консультация, редактирование текста

Скрипниченко Э.А. (ORCID ID: https://orcid.org/0000-0001-6321-8419): концепция статьи, обзор публикаций по теме, взаимодействие авторов

Эттингер О.А. (ORCID ID: https://orcid.org/0000-0002-1237-3731): научная консультация, редактирование текста

Паджева Т.М. (ORCID ID: https://orcid.org/0000-0003-0877-9672): научная консультация, редактирование текста

Никитин И.Г. (ORCID ID: https://orcid.org/0000-0003-1699-0881): редактирование текста, утверждение финального варианта статьи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Lyalina V.V. (ORCID ID: https://orcid.org/0000-0002-4262-4060): concept and design of the article, review of literature, authors interaction, text editing

Borisovskaya S.V. (ORCID ID: https://orcid.org/0000-0002-9365-1472): scientific advising, text editing

Skripnichenko E.A. (ORCID ID: https://orcid.org/0000-0001-6321-8419): concept of the article, review of literature, authors interaction

Ettinger O.A. (ORCID ID: https://orcid.org/0000-0002-1237-3731): scientific advising, text editing

Padzheva T.M. (ORCID ID: https://orcid.org/0000-0003-0877-9672): scientific advising, text editing

Nikitin I.G. (ORCID ID: https://orcid.org/0000-0003-1699-0881): text editing, approval of the final version of the article

Список литературы/ References:

1. Goodman S.M., Springer B., Guyatt G. et al. 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Antirheumatic Medication in Patients With Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty. Journal of Arthroplasty. 2017; 32(9): 2628-2638. doi: https://doi.org/10.1002/art.40149
2. Gualtierotti R., Parisi M., Ingegnoli F. Perioperative Management of Patients with Inflammatory Rheumatic Diseases Undergoing Major Orthopaedic Surgery: A Practical Overview. Advances in Therapy. 2018; 35(4): 439-456. doi: https://doi.org/10.1007/s12325-018-0686-0
3. Амирджанова В.Н. Клинические рекомендации по периоперационному ведению пациентов с ревматоидным артритом, нуждающихся в эндопротезировании крупных суставов нижних конечностей. Ассоциация ревматологов России. 2016; 8. [Электронный ресурс]. URL: https://rheumatolog.ru/experts/klinicheskie-rekomendacii. (дата обращения: 15.04.2021).
Amirdzhanova V.N. Clinical guidelines for the perioperative management of patients with rheumatoid arthritis requiring large joints arthroplasty. Russian Association of Rheumatologists. [Electronic resource]. URL: https://rheumatolog.ru/experts/klinicheskie-rekomendacii. (date of the application: 15.04.2021) [In Russian].
4. Strand V., Ahadieh S., French J. et al. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Research & Therapy. 2015; 17. doi: https://doi.org/10.1186/s13075-015-0880-2
5. Singh J.A., Cameron C., Noorbaloochi S. et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet. 2015; 386(9990): 258-265. doi: https://doi.org/10.1016/s0140-6736(14)61704-9
6. Bongartz T., Halligan C.S., Osmon D.R. et al. Incidence and Risk Factors of Prosthetic Joint Infection After Total Hip or Knee Replacement in Patients With Rheumatoid Arthritis. Arthritis & Rheumatism-Arthritis Care & Research. 2008; 59(12): 1713-1720. doi: https://doi.org/10.1002/art.24060
7. Hamrahian A.H., Roman S., Milan S. The management of the surgical patient taking glucocorticoids. 2019. [Electronic resource]. URL: https://www.uptodate.com/contents/the-management-of-the-surgical-patient-taking-glucocorticoids?topicRef=1826&source=see_link (date of the application: 15.04.2021).
8. Marik P.E., Varon J. Requirement of Perioperative Stress Doses of Corticosteroids A Systematic Review of the Literature. Archives of Surgery. 2008; 143(12): 1222-1226. doi: https://doi.org/10.1001/archsurg.143.12.1222
9. Тайлер К.Н., Дин К.Д. Периоперативное ведение пациентов с ревматическими заболеваниями. Секреты ревматологии. Дж.Уэст С. ГЭОТАР-Медиа. 2018; 111-118.
Tailer K.N., Din K.D. Perioperative management of patients with rheumatic diseases. Rheumatology Secrets. Sterling West GEOTAR-Media. 2018; 111-118 [In Russian].
10. Axelrod L. Perioperative management of patients treated with glucocorticoids. Endocrinology and Metabolism Clinics of North America. 2003; 32(2): 367. doi: https://doi.org/10.1016/s0889-8529(03)00008-2
11. Todd G.R. G., Acerini C.L., Ross-Russell R. et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Archives of Disease in Childhood. 2002; 87(6): 457-461. doi: https://doi.org/10.1136/adc.87.6.457
12. Tempark T., Phatarakijnirund V., Chatproedprai S. et al. Exogenous Cushing's syndrome due to topical corticosteroid application: case report and review literature. Endocrine. 2010; 38(3): 328-334. doi: https://doi.org/10.1007/s12020-010-9393-6
13. Duclos M., Guinot M., Colsy M. et al. High risk of adrenal insufficiency after a single articular steroid injection in athletes. Medicine and Science in Sports and Exercise. 2007; 39(7): 1036-1043. doi: https://doi.org/10.1249/mss.0b013e31805468d6
14. Kay J., Findling J.W., Raff H. Epidural triamcinolone suppress the pituitary-adrenal axis in human- subjects. Anesthesia and Analgesia. 1994; 79(3): 501-505. doi: https://doi.org/10.1213/00000539-199409000-00017
15. Habib G., Khazin F., Jabbour A. et al. Simultaneous Bilateral Knee Injection of Methylprednisolone Acetate and the Hypothalamic-Pituitary Adrenal Axis: A Single-Blind Case-Control Study. Journal of Investigative Medicine. 2014; 62(3): 621-626. doi: https://doi.org/10.2310/jim.0000000000000048
16. Lansang M.C., Farmer T., Kennedy L. Diagnosing the unrecognized systemic absorbtion of intra-articular and epidural steroid injections. Endocrine Practice. 2009; 15(3): 225-228. doi: https://doi.org/10.4158/ep.15.3.225
17. Hagg E., Asplund K., Lithner F. Value of basal plasma-cortisol assays in the assessment of pituitary-adrenal insufficiency. Clinical Endocrinology. 1987; 26(2): 221-226. doi: https://doi.org/10.1111/j.1365-2265.1987.tb00780.x
18. Schmidt I.L., Lahner H., Mann K., Petersenn S. Diagnosis of adrenal insufficiency: Evaluation of the corticotropin-releasing hormone test and basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. Journal of Clinical Endocrinology & Metabolism. 2003; 88(9): 4193-4198. doi: https://doi.org/10.1210/jc.2002-021897
19. Dekkers O.M., Timmermans J.M., Smit J.W. A. et al. Comparison of the cortisol responses to testing with two doses of ACTH in patients with suspected adrenal insufficiency. European Journal of Endocrinology. 2011; 164(1): 83-87. doi: https://doi.org/10.1530/eje-10-0621

20. Dickstein G., Saiegh L. Low-dose and high-dose adrenocorticotropin testing: indications and shortcomings. Current Opinion in Endocrinology Diabetes and Obesity. 2008; 15(3): 244-249. doi: https://doi.org/10.1097/med.0b013e3282fdf16d
21. Borst G.C., Michenfelder H.J., Obrian J.T. Discordant cortisol response to exogenous ACTH and ibsulin-induced hypoglycmia in patients with pituitary disease. New England Journal of Medicine. 1982; 306(24): 1462-1464. doi: https://doi.org/10.1056/nejm198206173062405
22. Wagner R.L., White P.F., Kan P.B. et al. Inhibition of adrenal steroidogenesis by the anecthetic etomidate. New England Journal of Medicine. 1984; 310(22): 1415-1421. doi: https://doi.org/10.1007/bf03315645
23. Murray H., Marik P.E. Etomidate for endotracheal intubation in sepsis — Acknowledging the good while accepting the bad. Chest. 2005; 127(3): 707-709. doi: https://doi.org/10.1378/chest.127.3.707
24. Амирджанова В.Н., Макаров М.А., Бялик Е.И. и др. Периоперационное ведение больных ревматоидным артритом. Научно-практическая ревматология. 2014; 52: 366-375. doi: http://dx.doi.org/10.14412/1995-4484-2014-366-375
Amirdzhanova V.N., Makarov M.A., Byalik E.I. et al. Perioperative management of patients with rheumatoid arthritis. Scientific and practical rheumatology. 2014. 52: 366-375. [In Russian] doi: http://dx.doi.org/10.14412/1995-4484-2014-366-375
25. Leopold S.S., Casnellie M.T., Warme W.J. et al. Endogenous cortisol production in response to knee arthroscopy and total knee arthroplasty. Journal of Bone and Joint Surgery-American Volume. 2003; 85A(11): 2163-2167. doi: https://doi.org/10.2106/00004623-200311000-00016
26. Huang Y.M., Wang C.M., Wang C.T. et al. Perioperative celecoxib administration for pain management after total knee arthroplasty — A randomized, controlled study. Bmc Musculoskeletal Disorders. 2008; 9. doi: https://doi.org/10.1186/1471-2474-9-77
27. Axford J.S. Preoperative evaluation and perioperative management of patients with rheumatic diseases. 2021. [Electronic resource]. URL: https://www.uptodate.com/contents/preoperative-evaluation-and-perioperative-management-of-patients-with-rheumatic-diseases#H11 (date of the application: 15.04.2021).