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Perioperative management of patients with inflammatory rheumatic diseases

Updated recommendations of the German Society for Rheumatology

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Abstract

Background: Prior to surgical interventions physicians and patients with inflammatory rheumatic diseases remain concerned about interrupting or continuing anti-inflammatory medication. For this reason, the German Society for Rheumatology has updated its recommendations from 2014.

Methods: After a systematic literature search including publications up to 31 August 2021, the recommendations on the use of of glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologics (bDMARDs) were revised and recommendations on newer drugs and targeted synthetic (ts)DMARDs were added.

Results: The glucocorticoid dose should be reduced to as low as possible 2–3 months before elective surgery (in any case <10 mg/day) but should be kept stable 1–2 weeks before and on the day of surgery. In many cases csDMARDs can be continued, exceptions being a reduction of high methotrexate doses to ≤15 mg/week and wash-out of leflunomide if there is a high risk of infection. Azathioprine, mycophenolate and ciclosporin should be paused 1–2 days prior to surgery. Under bDMARDs surgery can be scheduled for the end of each treatment interval. For major interventions Janus kinase (JAK) inhibitors should be paused for 3–4 days. Apremilast can be continued. If interruption is necessary, treatment should be restarted as soon as possible for all substances, depending on wound healing.

Conclusion: Whether bDMARDs increase the perioperative risk of infection and the benefits and risks of discontinuation remain unclear based on the currently available evidence. To minimize the risk of a disease relapse under longer treatment pauses, in the updated recommendations the perioperative interruption of bDMARDs was reduced from at least two half-lives to one treatment interval.

Keywords
Operation · Glucocorticoids · Disease-modifying antirheumatic drugs · Biologics · Infection risk

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All authors write for the Pharmacotherapy Commission of the German Society for Rheumatology (DGRh) and the Board of Directors of the DGRh.

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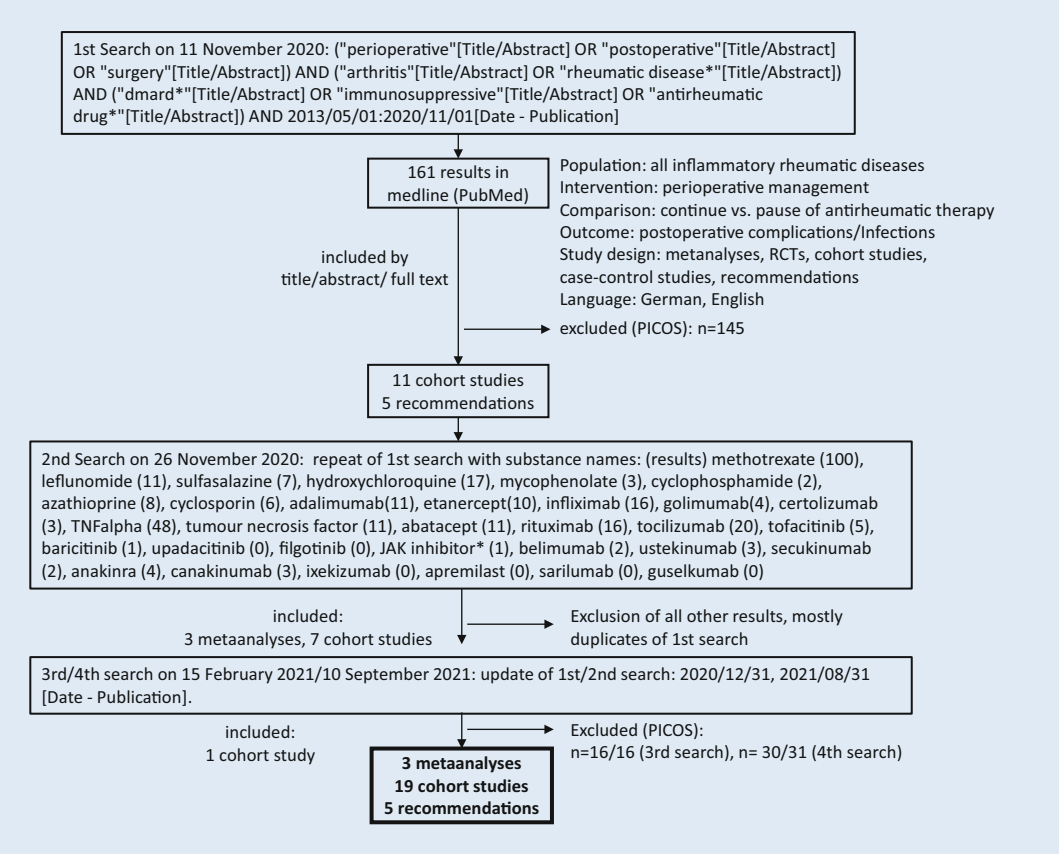

Fig. 1 ◀ Systematic literature search on perioperative therapy for inflammatory rheumatic diseases. Searches used the PICOS (population, intervention, comparison, outcome, study design) search strategy. *RCT* randomized controlled trial

The perioperative management of patients with inflammatory rheumatic diseases remains a complex challenge due to the variety of immunosuppressive and immunomodulatory therapies currently used. Data from the national database of the German Collaborative Arthritis Centers show that the number of patients with rheumatoid arthritis (RA) requiring surgical joint interventions has decreased by more than 50% over the past 20 years [1]. Nevertheless, rheumatology patients may still require a number of other orthopedic and surgical interventions, thus raising the question of perioperative continuation or pausing of anti-inflammatory therapy. This important interdisciplinary topic is relevant to both rheumatological and surgical care.

In 2014, the German Society for Rheumatology (*Deutsche Gesellschaft für Rheumatologie*, DGRh) formulated recommendations on perioperative procedures for patients with inflammatory rheumatic diseases, including recommendations regarding perioperative interruption or continuation of each of the conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs) [2]. Since then, additional agents not covered by previous recommendations, including targeted synthetic DMARDs (tsDMARDs) such as Janus kinase (JAK) inhibitors and the phosphodiesterase (PDE)4 inhibitor apremilast as well as some interleukin (IL) blockers, have been approved and are being used as new treatments for rheumatic diseases. The perioperative use of these newer agents was discussed in a 2017 literature review [3]. International recommendations for the perioperative management of hip and knee replacements in patients with RA, axial spondyloarthritis, psoriatic arthritis, and systemic lupus erythematosus were published in 2017 joint guidelines from the American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons [4]. These guidelines were reviewed in 2020 [5]. The European League Against Rheumatism (EULAR) has not published any recommendations to date. Therefore, the DGRh commissioned the Pharmacotherapy Committee to update the national recommendations on perioperative DMARD therapy.

Methods

A systematic literature search was conducted for the period from 01 May 2013 (end of the systematic literature review of the previous recommendations) to 31 August 2021. Inclusion criteria are listed in ◘ **Fig. 1**. The following substances were considered: glucocorticoids (GCs), csDMARDs (methotrexate [MTX], leflunomide, sulfasalazine, hydroxychloroquine, azathioprine, cyclosporin A, mycophenolate, cyclophosphamide), tumor necrosis factor (TNF) inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab), the T-cell costimulation blocker abatacept, the B-cell depletor rituximab, IL-1 inhibitors anakinra and canakinumab, IL-6 receptor inhibitors sarilumab and tocilizumab, IL-17 inhibitors ixekizumab and secukinumab, IL-23 (and IL-12/23) inhibitors guselkumab and ustekinumab, the B-lymphocyte stimulator (BLyS) inhibitor belimumab, JAK inhibitors (barici-

Table 1 Factors influencing the risk of perioperative infections. (Modified according to [6])
Inflammatory rheumatic disease
Current disease activity, disease duration/progression, severity, GC requirement >10 mg
Patient-related factors
Older age, male gender, smoking, alcohol consumption, malnutrition
Comorbidities including anemia, obesity, diabetes, chronic lung diseases
Previous infections
Skin lesions, skin contamination, psoriatic plaques
Surgical procedure
Type, size, duration, localization

tinib, filgotinib, tofacitinib, upadacitinib), and the PDE4 inhibitor apremilast. Three meta-analyses, 19 cohort studies, and five recommendations were included. The identified publications were assigned to the therapeutic substances and compared with the previous German and international recommendations. The previous German and ACR recommendations were selected as reference recommendations and checked for congruence. From these and the newly added literature, the recommendations were updated and formulated by consensus. Ten commission members rated each core recommendation with their agreement or disagreement and the degree of agreement on a numerical rating scale (degree 0 = disagree, degree 10 = fully agree). The recommendations were reviewed and approved by the Executive Board of the DGRh.

General recommendations

Patients with inflammatory rheumatic diseases may have an increased risk of perioperative infections [6]. The individual risk of complications largely depends on the condition of the underlying rheumatological disease (**Table 1**). Higher disease activity, longer disease duration, and a more severe disease course contribute to a higher risk of infection, whereas well-controlled disease is associated with a lower risk of infection and with a lower requirement for GCs.

For elective surgery, the rheumatic disease should be controlled in advance to the greatest extent possible, including the use of bDMARDs, if needed. Smoking, alcohol consumption, and malnutrition increase the risk of complications; these contributors should also be addressed in advance. Comorbidities, especially previous infections, obesity, diabetes mellitus, anemia, and chronic lung disease are other risk factors that can be modified by prior optimization (e.g., body mass index <40 kg/m^2, HbA1c <7%, transfusion) before elective surgery [6]. The management of osteoporosis, which is common in rheumatic diseases, should also be optimized, as concomitant osteoporosis increases the risk of position-related fractures and may reduce the stability of osteosyntheses [7]. Further, preoperative treatment of skin lesions and measures to limit skin contamination with *Staphylococcus* or *Streptococcus* spp. may reduce the risk of germ transmission [6].

» Inflammatory rheumatic diseases carry an increased risk of perioperative infections

Prior periprosthetic infections constitute a substantial risk factor for future prosthetic infections. In patients who had an infected prosthesis after knee or hip replacement, the risk of re-infection with another arthroplasty at a different joint was increased threefold in a case-control study, suggesting that these patients require special caution [8]. Because bacterial contamination is to be expected in oral surgical procedures, antibiotic prophylaxis is recommended [9]. In this case, the immunomodulatory and immunosuppressive effects of antirheumatic therapy on infection risk and wound healing are considered higher than in aseptic surgery, so a discontinuation of treatment may also be reasonable [10].

Overarching recommendations

The working group fully agreed with the overarching recommendation that the decision on whether and for how long to pause antirheumatic therapy during elective surgery needs to be made depending on the individual risk of infection and the risk of a disease flare. Urgent or emergency surgery should be performed promptly or immediately regardless of ongoing DMARD therapy. To minimize the risk of relapse, interruption of antirheumatic therapy should be as brief as possible and therapy should be restarted as soon as wound conditions are stable (**Table 2**). In patients with high rheumatic disease activity, elective surgery should not be performed until stabilization of the rheumatic disease has been achieved.

Recommendations for specific therapeutic agents

The available evidence for all recommendations must be classified as low and is mainly based on retrospective studies or, in the absence of data, on expert opinion.

Glucocorticoids

Recent larger studies [11–14] confirm data underlying previous recommendations [15, 16] indicating a dose-dependent increased risk of perioperative complications, especially infections, with GCs. A retrospective study based on health insurance data from 10,923 RA patients undergoing elective knee or hip replacement showed that the risk of infections leading to hospitalization within 30 days postoperatively was significantly higher in patients receiving 5–10 mg prednisone equivalent/day (OR 1.32) and >10 mg/day (odds ratio [OR] 2.10) compared to patients not receiving GC therapy. The risk of prosthetic joint infections within 1 year was numerically higher for patients treated with 5–10 mg prednisone equivalent/day (hazard ratio [HR] 1.36) and significantly higher for >10 mg/day (HR 1.86) [11]. Supplementary data from a methodologically comparable study of 10,483 RA patients undergoing other major surgeries (hip fracture osteosynthesis, abdominal/pelvic or cardiac surgery) showed significantly increased risks in terms of adjusted 90-day mortality and 30-day re-hospitalization with GC 5–10 mg/day (OR 1.41 and OR 1.26) and >10 mg/day (OR 1.64 and OR 1.60) [12]. In a Danish registry-based cohort study, GC was also identified (in addition to increased disease activity) as a risk factor for mortality after knee/hip replacement (HR 2.87) [13]. In another

Table 2 Core recommendations for perioperative management of antirheumatic therapy

		LoE	Consent	Degree of agreement
Overarching recommendations				
A.	In principle, when deciding whether and for how long to pause antirheumatic therapy perioperatively, the individual risk of infection (including older age, multimorbidity, previous infections) should be weighed against the risk of a disease flare of the underlying rheumatic disease (highly active or well adjusted, GC requirement)	–	10/10	9.9
B.	Urgent/emergency surgery should be performed promptly/immediately regardless of DMARD therapy use	–	10/10	10.0
C.	If therapy is interrupted perioperatively, all necessary antirheumatic therapies should be restarted as soon as possible when there are no signs of infection and the wound conditions are normal	–	10/10	9.9
D.	Treatment interruptions of antirheumatic drugs with a short half-life should not exceed 14 days, if possible, in order to avoid disease relapse	–	10/10	9.5
Recommendations for specific drugs				
1.	GCs should be reduced to the lowest possible dose in the 2–3 months before surgery, at least <10 mg prednisolone equivalent/day for elective surgery. Perioperatively, the GC dose should remain constant	4	10/10	9.2
2.	MTX may be continued. If the dose is high (>20 mg/week), consider temporary dose reduction	4	10/10	9.6
3.	Leflunomide can be continued if the risk of infection is low. If the risk of infection is high, leflunomide should be "washed out" (eliminated at an accelerated rate) preoperatively	3.5	10/10	9.4
4.	Hydroxychloroquine and sulfasalazine may be continued perioperatively	4	10/10	10.0
5.	Azathioprine, cyclosporin A and mycophenolate should be paused 1–2 days before surgery. If the risk of a relapse is high, therapy should be continued	5	10/10	9.4
6.	TNF inhibitors, IL-1, IL-6, IL-17, IL-23, and IL-12/23 inhibitors, abatacept and belimumab should be paused perioperatively during major elective surgery or when there is an increased risk of infection, and surgery should be scheduled at the end of the respective therapy interval (except for anakinra, see 7)	4	10/10	9.7
7.	With anakinra, a 1–2-day break before surgery is sufficient	5	10/10	9.8
8.	Elective surgery under rituximab can be scheduled 4 months after the last infusion and at least 4 weeks before the next infusion	5	10/10	8.8
9.	JAK inhibitors should be paused 3–4 days before surgery for major procedures	4	10/10	9.4
10.	Apremilast can be continued	5	9/10	9.7

The level of agreement (0 = no agreement, 10 = full agreement) is given as a mean value
DMARD disease-modifying antirheumatic drugs, *GC* glucocorticoid, *IL* interleukin, *JAK* Janus kinase, *LoE* level of evidence according to the Oxford Centre for Evidence-Based Medicine [67], *MTX* methotrexate, *TNF* tumor necrosis factor

retrospective analysis of 14,774 patients undergoing long-term GC therapy for various chronic conditions, significantly more perioperative complications, including wound infections, deep surgical infections, wound dehiscence, pneumonia, urinary tract infections, and re-hospitalization, were found in patients receiving GC compared with patients without GC according to a univariate analysis [14].

» There is a dose-dependent increased risk of perioperative infections

In summary, the studies show a dose-dependent increase in the postoperative risk of infection in patients treated with GCs. Starting at a dose of >10 mg prednisolone equivalent/day during the preoperative period (usually the preceding 3 months), consistent, highly significant increases in risk were observed for postoperative infections and additional complications such as re-hospitalization and mortality. Based on these data, the GC dose should be as low as possible in the 3 months before elective surgery—less than 10 mg/day at least—if treatment of the inflammatory disease permits. Minimizing GC dose in the months before surgery may improve outcomes, and postponement of surgery may be appropriate in certain situations, especially in patients receiving high doses of GC. In elective surgery known well in advance, guideline-based adjustment of treatment to reduce or avoid GC in advance of surgery is desirable given the lower risk for csDMARDs and bDMARDs compared with GC >10 mg/day.

In contrast to long-term reductions in GC doses, a reduction of the risk by a short-term preoperative dose reduction has not yet been proven and current data do not support a recommendation to reduce the GC dose to ≤10 mg prednisolone equivalent/day a few days before surgery. Consequently, the GC dose that patients receive for their inflammatory rheumatic disease should be kept constant in the period immediately preceding surgery (approximately 1–2 weeks). Another concern regarding short-term preoperative GC dose reduction, which has also been addressed in previous recommendations [2–4], is perioperative hemodynamic instability/hypotension due to adrenal insufficiency with a physiologically higher cortisol demand as a consequence of surgery-related stress. In this regard, it

can be further assumed that an increased supraphysiological perioperative dose ("stress prophylaxis," e.g., with hydrocortisone) is not necessary with continuous GC therapy up to 20 mg/day and, moreover, the measurement of cortisol levels is not helpful [17]. Patients should therefore receive only the usual GC daily dose on the day of surgery.

Methotrexate

For methotrexate (MTX), results are available from two randomized controlled trials that showed no increased (and even a decreased) risk of infection with MTX therapy in patients with RA undergoing orthopedic joint surgery [18, 19]. Similarly, patients with inflammatory bowel disease who underwent abdominal surgery showed no increased risk of postoperative complications (including infections and wound healing disorders) with existing preoperative MTX therapy [20]. Thus, treatment with MTX can be continued perioperatively. This also reduces the risk of worsening/relapse of the underlying disease [18]. The same is recommended by the American guideline on perioperative use of drugs in patients with rheumatologic diseases [4]. However, it should be mentioned that high doses of MTX (>20 mg/week) have not been explicitly studied, so a temporary reduction of the dose to ≤15 mg/week should be considered. A postponement of the weekly injection can be considered if there are concerns about possible interactions or additive hepatotoxicity with drugs to be used perioperatively.

Leflunomide

For leflunomide, the evidence for a risk of postoperative infections is not clear. While in one study leflunomide was not associated with an increased risk of infections after total joint arthroplasty in patients with RA [21], another study showed an increased risk of wound healing disorders [22]. Because there are still no randomized controlled trials available, we remain with the pragmatic approach of the previous national guidelines [2]: continue leflunomide for a low risk of infection and minor procedures, but employ washout procedures for accelerated elimination (8 g cholestyramine 3 × daily or 50 g activated charcoal powder 4 × daily for 5 days) for a high risk of infection or major procedures. Treatment can be restarted after appropriate wound healing. Due to a long half-life of up to 4 weeks and persistence of the active metabolite teriflunomide by enterohepatic recirculation for up to 2 years, simple discontinuation of leflunomide immediately before the planned procedure without a washout procedure is not advisable.

Sulfasalazine

In a retrospective cohort study of 768 patients and 1219 elective procedures, sulfasalazine was associated with no increased risk of complications, including infections, but rather a decreased risk [23]. It can be assumed that sulfasalazine does not have a significant immunosuppressive effect and thus does not increase the risk of infection. Accordingly, the American recommendations also consider perioperative interruption unnecessary [4]. However, because of its relatively short half-life (6–8 h), sulfasalazine could be discontinued the day before surgery and restarted promptly after surgery if there are justified concerns about possible interactions and additive hepatotoxic effects.

Hydroxychloroquine

There are still insufficient data on the perioperative management of chloroquine and hydroxychloroquine; chloroquine is rarely used. Based on the rationale that these substances are not associated with potent immunosuppression, they can be continued perioperatively. In addition, the long half-life of 40–50 days argues against interruption. Perioperative continuation of hydroxychloroquine is also recommended in the American guideline [4]. However, in case of justified concerns regarding side effects or potential interactions (e.g., QT interval prolongation, especially at higher doses), a short-term perioperative interruption is also possible due to the immunological effect exceeding the half-life, without an immediate disease flare-up being expected.

Azathioprine, cyclosporin A, mycophenolate

For these substances, currently available data do not allow an evidence-based recommendation. These drugs are mainly used in patients with severe systemic diseases such as connective tissue diseases (particularly systemic lupus erythematosus) or vasculitides. A potential immunosuppressive effect of these drugs with a possible influence on the risk of infection led to the stratification of patients according to the severity of the underlying disease in the ACR recommendations [4]: it was argued that in patients with severe, inadequately controlled disease, the risk of worsening of the underlying disease outweighs, which is why treatment with the named substances should be continued. Since all of these drugs have a short half-life (azathioprine 4–5 h, cyclosporin A 5–10 h, mycophenolate approximately 16 h), the substances should no longer have an immediate effect on the perioperative situation if there is a short pause of 1–2 days before surgery, even if the immunosuppressive effect lasts longer. The risk of relapse of the inflammatory rheumatic disease is unlikely to be relevant with such a short interruption, which is why we maintain the recommendation to pause these drugs for a short time.

Tumor necrosis factor inhibitors

The evidence base regarding perioperative risk during TNF inhibitor (TNFi) therapy has not improved substantially since the previous DGRh perioperative recommendations. There are still no prospective randomized controlled studies; available data are mainly from retrospective cohort studies and a few retrospective case-control studies. The individual studies are not comparable with each other because factors such as case numbers, the type of interventions investigated, DMARD discontinuation times, or the definition of infectious events differ. In most studies, no adjustments were performed for relevant cofactors such as activity and duration of the underlying disease, existing comorbidities, or concomitant GC therapy, and in many cases these cofactors were not even described.

Therefore, three meta-analyses published in recent years [24–26] should be interpreted with caution due to methodological aspects. In part, these meta-analyses refer to the same publications, resulting in a high degree of overlap. Clay et al. evaluated six studies with 2743 patients, comparing the risk of wound infections in 1360 patients with continued and 1383 with interrupted TNFi therapy [24]. The discontinuation time of TNFi varied, as did the type of intervention. Concomitant therapies and characteristics of the underlying diseases were not recorded, and the follow-up also varied. Two of the studies had very large case numbers and four studies had small case numbers. Discontinuation times ranged from 4 to 8 weeks for infliximab, 2 to 8 weeks for adalimumab, and 1 to 2 weeks for etanercept. A TNFi pause was associated with a significant risk reduction for perioperative infections (risk ratio [RR] 0.62), as well as for general complications (RR 0.60). Two studies also assessed the risk of relapse during the TNFi pause, which was significantly increased fivefold (RR 5.02).

In their meta-analysis, Mabille et al. initially included 12 studies for a comparison of postoperative infection risk in 4975 procedures under TNFi therapy vs. 61,090 in a control group under csDMARDs; five of the studies from the analysis by Clay et al. were also included [26]. Individually, only four of 12 studies found a significantly higher risk under TNFi, six showed a trend, and two found no difference in risk. In the meta-analysis, the risk ratio under TNFi was significantly increased (RR 1.81). Another meta-analysis including only seven of the studies compared interruption and continuation of TNFi therapy and found no significant difference in the risk of infection.

In a third meta-analysis, Goodman et al. evaluated the results from eight observational and three case-control studies, all of which were retrospective, again showing overlap with the other two meta-analyses [25]. Compared were 3681 patients with and 4310 without TNFi exposure in the perioperative period. All of the above weaknesses also applied to most of the studies evaluated in this publication, each to varying degrees. The analysis showed a significantly increased risk of infection with an OR of 2.47 for the TNFi-exposed patients. An optimal time period for pausing TNFi therapy could not be determined in this meta-analysis due to the heterogeneity of the results.

The Japanese study by Kubota et al. provides an example of the potential benefit of adjusting for relevant cofactors before determining risk [27]. In this study, 267 patients with and 300 without bDMARD therapy ($n = 245$ with TNFi) were retrospectively compared, adjusting for age, disease duration, prednisolone use, and type of surgery. After adjustment, the risk of infection was not increased with bDMARD therapy.

A number of other studies on this topic were published after the meta-analyses appeared. In a Swedish study, data from 494 arthroplasty procedures were retrospectively evaluated [28]. Among them were 157 patients with TNFi therapy. Only 19 cases (3.8%) of wound infection occurred, and no relation to DMARD therapy (including TNFi) was found. In addition, there were seven cases (1.4%) of prosthesis infections, including only one case in a patient with ongoing TNFi therapy.

A retrospective cohort study based on American insurance data investigated 4288 endoprosthetic procedures in patients treated with infliximab [29]. Infections with hospitalization within 30 days occurred in 270 cases (6.3%). Discontinuation of infliximab within 4 weeks before surgery was compared with a longer discontinuation period; there was no difference, i.e., no advantage, with a longer discontinuation period. In another retrospective cohort study by the same research group, the risk of infections with hospitalization within 30 days, as well as the risk of prosthesis infection within 1 year, was investigated in 9911 patients treated with various bDMARD therapies who underwent 10,923 procedures [11]. Infections with hospitalization occurred with similar frequency in the range of 6.8–9.0% among the individual bDMARDs, and the differences in prosthesis infections were also small.

A different approach was used by an American research group for 1818 elderly patients treated with infliximab and undergoing cardiovascular and intestinal procedures [30]. This group studied the impact of different intervals between the last infliximab administration and surgery (ranging from 0 to 90 days) on wound and other types of infections. The interval did not play a role in the occurrence of infections.

» It is not proven that ongoing TNFi therapy increases the perioperative risk

In summary, the picture regarding the current evidence is heterogeneous. It cannot be safely assumed that ongoing TNFi therapy increases the perioperative risk. From general studies on the risk of serious infectious events in patients on DMARD therapy, we know that other factors such as the activity of the underlying disease, comorbidities, or concomitant GC therapy have a greater impact on the risk of serious infections than TNFi therapy [31]. However, the studies presented here did not rigorously consider these influencing factors. Thus, it is still not possible to determine the actual risk associated with TNFi therapy.

In particular, no evidence can be found that the length of the discontinuation period determines the risk of infection. Even the most recent Japanese meta-analysis from 2021 [32] only distinguishes between bDMARD versus no bDMARD therapy and does not differentiate between perioperative interruption vs. continuation; thus, no recommendations can be derived from these data. Unfortunately, only two studies assessed the risk of flares in case of a long discontinuation, and both identified a substantial increase in risk. Based on these data, it does not seem justified to continue to recommend a treatment interruption period of two half-lives for TNFi therapy before major surgery. Therefore, in accordance with current American recommendations, we recommend a treatment pause of only one dosing interval before major interventions and in the presence of other individual risk factors, i.e., a shortening of the originally recommended TNFi-related pause of two half-lives. This change seems justified given the absence of new negative evidence in the past 8 years of additional experience.

Table 3 Usual treatment intervals of biologic disease-modifying antirheumatic drugs (bDMARDs)

	Treatment interval
TNF inhibitors	
Etanercept	Weekly 50 mg, twice weekly 25 mg
Adalimumab	2 weeks
Certolizumab	2 weeks
Golimumab	s.c. 4 weeks, i.v. 8 weeks
Infliximab	6–8 weeks
T-cell costimulation blocker	
Abatacept	s.c. weekly, i.v. 4 weeks
B-cell depletion	
Rituximab	4–6 months
IL-1 inhibitors	
Anakinra	Daily
Canakinumab	Usually 4 weeks
IL-6 receptor inhibitors	
Sarilumab	2 weeks
Tocilizumab	s.c. weekly, i.v. 4 weeks
IL-17 inhibitors	
Ixekizumab	4 weeks
Secukinumab	4 weeks
IL-23 (and IL-12/23) inhibitors	
Guselkumab	8 weeks
Ustekinumab	12 weeks
BLyS inhibitor	
Belimumab	i.v. 4 weeks, s.c. weekly

TNF tumor necrosis factor, *IL* interleukin, *BLyS* B lymphocyte stimulator

Abatacept

Three recent studies provide no evidence that a longer pause of abatacept reduces the risk of perioperative complications. In the French Orencia RA registry, which included 205 patients undergoing 263 surgical procedures (67% orthopedic), the median duration between the last abatacept infusion and surgery was 5.9 weeks (0.3–12.0 weeks), with no significant difference between patients with or without postoperative complications, including infections and wound healing disorders [33]. In a retrospective case-control study from Japan, orthopedic surgery patients treated with abatacept vs. csDMARDs ($n = 97$ each) were compared with respect to postoperative complications. Comparisons of the time of perioperative pause of abatacept (<6 vs. ≥7 days, <14 vs. ≥14 days) and the mode of administration (intravenous vs. subcutaneous) found no differences in complication rates [34]. US insurance data examined the impact of the time interval between the last abatacept administration and a knee or hip replacement in 1780 patients. The rate of hospitalized infections (9%), periprosthetic joint infections (2.4/100 periprosthetic joints), and inpatient readmissions (6.3%) did not differ significantly with continuous (<4 weeks) vs. paused administration (4–8 weeks or ≥8 weeks) [35]. These data suggest that the duration of treatment interruption may well be reduced without accepting greater risk. Analogous to our American colleagues [5], we recommend planning surgery for abatacept at the end of the treatment interval (**Table 3**).

Rituximab

For B-cell depletion with rituximab, only one retrospective cohort study is available from the French AIR registry [36]. Of 133 patients, 94 orthopedic and 23 abdominal procedures were evaluated, and 9 patients had postoperative complications (8.5%). The median duration between the last infusion and surgery was 6.4 months (interquartile range 4.3–8.7 months) and did not differ relevantly between patients with or without complications. Data on immunoglobulin levels were not available. With insufficient data, we recommend scheduling elective procedures 4 months after the last infusion and at least 4 weeks before the next infusion. Since low immunoglobulin levels increase the risk of infection [37], preoperative determination of immunoglobulin levels—particularly in cases with a high risk of infection or recurrent infections due to other risk factors and the type of surgery—could be useful, with consideration of immunoglobulin prophylaxis if levels are below 4 g/L [38, 39] and surgery is within 3 weeks after immunoglobulin administration.

Interleukin-6 receptor inhibitors

In the REGATE registry for the IL-6 receptor inhibitor tocilizumab including 167 patients with 165 surgeries (59% orthopedic), 15 complications occurred, 10 of which were serious. As with rituximab, there were no significant differences in the mean time intervals (4.94 ± 1.74 weeks) between the last tocilizumab infusion and surgery in patients with or without complications [40]. It is important to note that tocilizumab suppresses the warning signs of postoperative infection (fever and C-reactive protein increases), but has no effect on the change in leukocyte count [41]. A comparative analysis of US Medicare data showed no differences in rates of hospitalized infections, periprosthetic joint infections, and inpatient readmissions among abatacept, adalimumab, etanercept, infliximab, rituximab, or tocilizumab [11]. However, the lower case numbers for tocilizumab ($n = 389$) and rituximab ($n = 423$) limit the interpretation of this finding. There are currently no data on sarilumab. With uncertain data, for the time being, the recommendation remains to pause tocilizumab and sarilumab perioperatively, analogous to the other bDMARDs.

Interleukin-1, 17, 12/23, 23, and BLyS inhibitors

For the other IL inhibitors—anakinra, canakinumab, ixekizumab, secukinumab, guselkumab, and ustekinumab—and the BLyS inhibitor belimumab, there are still no data on perioperative use. Pragmatically and analogous to the other bDMARDs, we recommend scheduling the planned surgery at the end of the respective treatment interval (**Table 3**). Since anakinra has a very short half-life (4–6 h), a pause of 1–2 days before surgery is sufficient.

Targeted synthetic DMARDs

The group of targeted synthetic DMARDs (tsDMARDs) or "small molecules" includes (as of September 2021) one PDE4 inhibitor (PDE4i) and four JAK inhibitors (JAKi), which have different approval spectrums. All five approved drugs are administered orally and have a short half-life (see **Table 4**), which makes them easy to control before and after surgery and could theoretically be advantageous in terms of perioperative risk (including wound healing and infection). However, as these agents are still relatively new, the evidence regarding this risk among tsDMARDs is very limited and there are no prospective randomized controlled tri-

Table 4 Half-lives of the targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs)

	Mean half-life with normal kidney or liver function
JAK inhibitors	
Baricitinib	Approximately 12 h
Filgotinib	Approximately 7 h
Tofacitinib	Approximately 3 h (retard approximately 6 h)
Upadacitinib	Approximately 9–14 h
PDE inhibitors	
Apremilast	Approximately 6–9 h

JAK Janus kinase, *PDE* phosphodiesterase

als. Currently available evidence includes retrospective data from a case series describing 9 patients with RA who were treated with tofacitinib and underwent orthopedic surgery [42], and data from the Medicare study [12] in which there was no increased risk of adjusted 90-day mortality and 30-day re-hospitalization with non-TNF bDMARDs or tsDMARDS ($n = 29$ patients treated with tofacitinib). In a retrospective review of 53 patients with ulcerative colitis who had received tofacitinib within 4 weeks prior to abdominal colorectal surgery, rates of postoperative complications occurring within 90 days of surgery were determined. A total of 20 patients (37.7%) experienced postoperative complications, 6 patients (11%) experienced infection-related complications, and 7 patients (13.2%) experienced venous thromboembolism [43]. Due to the limited data, the ACR was also only able to make a recommendation based on indirect evidence from a meta-analysis on the overall risk of infection for tofacitinib vs. placebo or csDMARDs in their 2017 recommendations, and recommended a pause of 7 days before planned surgery [4]. Since JAKi increase the risk of venous thromboembolism [44], a pause also seems reasonable for this reason. In our opinion, a 3–4-day pause before surgery is sufficient. Regarding apremilast, Italian authors of a 2018 review recommend pausing apremilast 3 days before surgery due to its short half-life [45]. There are no further data on this. According to the expert opinion of the DGRh, apremilast can be continued perioperatively. If paused, all tsDMARDs should be restarted as soon as possible when wound conditions are stable. Although randomized controlled trial data show that a short-term interruption of therapy with baricitinib (in most cases ≤2 weeks) does not lead to a sustained worsening of the clinical situation [46], treatment should be resumed within 3–5 days if possible due to the very short half-life. Under certain circumstances, even a few days of interrupted treatment may be sufficient to trigger a relapse. Therefore, a total break of 14 days perioperatively should not be exceeded, if possible.

Discussion

Patients with inflammatory rheumatic diseases have an increased risk of postoperative complications, particularly infections after joint replacement [13, 47, 48]. With this in mind, the management of antirheumatic medications that could potentially increase this risk is an important decision that many physicians and patients face at some point during the course of the rheumatic disease. Since the introduction of bDMARD therapies in the early 2000s, surgical interventions have fortunately decreased, not only in Germany but also in many other countries [49–53]. Nevertheless, surgical interventions are still more frequent in patients with inflammatory rheumatic diseases than in the healthy population [54]. Complications following surgery, on the other hand, appear to be declining over time. According to data from a systematic review of 44 studies on hip arthroplasty, the complication rate decreased by one half, from 10% in the 1990s to 5% in the 2010s. However, this was mainly related to revisions and periprosthetic fractures, while infections were more common, along with aseptic loosening [55]. The risk of infection therefore remains central in the assessment of whether antirheumatic therapy should be paused or continued perioperatively.

For recommendations regarding the duration of pausing antirheumatic drugs, we considered both the drug half-life and the assumed immunological duration of action. For some agents, especially the csDMARDs but also certain bDMARDs (e.g., rituximab) and JAKi, immunological effects can extend beyond the half-life, so half-lives are a useful guide, but not always identical to the persistence of the immunological effect.

With regard to GC, we recommend setting the lowest possible dose in advance, which should then be kept stable perioperatively. For csDMARD therapies, we have retained the dose reduction of methotrexate to >20 mg/week and leflunomide "washout" if the risk of infection is high. For azathioprine, mycophenolate, and cyclosporin A, we continue to recommend a 1–2-day preoperative pause. In accordance with the updated American recommendations [5] and based on the updated literature review, we recommend a treatment pause of only one dosing interval before major surgery and in the presence of other individual risk factors for bDMARD therapies. For JAKi therapies, we consider a 3–4-day pause to be sufficient for major surgery. Apremilast can be continued perioperatively.

Overall, there is increasing evidence that continuation of bDMARDs during the perioperative period is possible in many cases. In the absence of randomized trials, health insurance data are increasingly being evaluated for this question. These data give rise to cautious optimism that perioperative continuation of bDMARD therapy does not increase the postoperative risk of infection [11, 29, 35, 56]. In a Swedish hospital in Lund, TNFi and most other bDMARDs have not been routinely interrupted perioperatively since 2009. In the most recent study at this center, the infection rate was not increased, so the clinic maintains continuation of these agents before surgery [28]. Especially in view of the high infection risk of GC therapy, prolonged pausing of bDMARDs may actually be unfavorable, especially if this leads to a disease flare requiring higher-dose GC therapy.

» Continuation of bDMARDs is possible in many cases

Another rationale for continuing treatment is frequent disease relapse within 6 weeks after hip or knee replacement [57]. On the other hand, no effect on function and pain at 1 year has been observed with postoperative relapses [58], so it is debat-

able whether postoperative relapses can be tolerated as long as disease activity is not persistently high. A recently published small case-control study reported an increased likelihood of periprosthetic infections after total arthroplasty in 26 patients who continued biologic therapy compared with 58 patients who paused therapy [59]. Therefore, further data are awaited in order to be able to better answer the question of pausing or continuing bDMARD therapy prior to surgery.

In addition to the most common surgical procedures of knees and hips, there are also studies with smaller numbers of cases that show no increased complication rates for procedures involving shoulder, foot and ankle, and spine during antirheumatic therapy [60–62]. Similarly, for hand surgery, there were no increased complications in patients who continued DMARD therapy, but this included few patients on bDMARDs [63]. For spinal deformity corrections, RA patients had a higher complication rate overall, particularly pulmonary thromboembolism [64]. In a small study of 39 RA patients who underwent cervical arthrodesis, there were no increased complications when DMARD therapy was continued ($n = 19$) [65]. However, there are no specific recommendations for spinal procedures. Expert opinion advises interruption of DMARDs analogous to the ACR recommendations [66].

Practical conclusion

- **The perioperative risk of infection is a multifactorial event, but drug therapy is a major modifiable factor.**
- **Whether biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) increase the risk of infection perioperatively, and what role the discontinuation period plays in this, remains unclear with the current evidence.**
- **However, it is certain that glucocorticoids, especially in doses above 10 mg/day, significantly increase the risk of infection. Therefore, in the updated recommendations of the German Society for Rheumatology (DGRh), the perioperative pause of bDMARDs has been reduced from at least two half-lives to one treatment interval in order to minimize the risk of disease relapse during prolonged therapy interruption.**
- **The newer small molecules such as Janus kinase inhibitors (JAKi) have very short half-lives and should not be paused perioperatively for an extended period in order to avoid disease relapses.**

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Declarations

Conflict of interest. K. Albrecht, D. Poddubnyy, J. Leipe, P. Sewerin, C. Iking-Konert, R. Scholz, and K. Krüger declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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Zusammenfassung

Perioperativer Umgang mit der Therapie von Patienten mit entzündlich rheumatischen Erkrankungen. Aktualisierte Empfehlungen der Deutschen Gesellschaft für Rheumatologie. Englische Version

Hintergrund: Vor operativen Eingriffen stellt sich Ärzten und Patienten mit entzündlich rheumatischen Erkrankungen weiterhin die Frage nach einer Unterbrechung oder Fortsetzung der entzündungshemmenden Medikation. Die Deutsche Gesellschaft für Rheumatologie hat hierfür ihre Empfehlungen von 2014 aktualisiert.
Methoden: Nach einer systematischen Literaturrecherche mit Einschluss von Publikationen bis zum 31.08.2021 wurden die Empfehlungen zum Umgang mit Glukokortikoiden, konventionell synthetischen „disease-modifying antirheumatic drugs" (csDMARDs) und Biologika (bDMARDs) überarbeitet und Empfehlungen zu neueren Substanzen und „targeted synthetic (ts) DMARDs" ergänzt.
Ergebnisse: Die Glukokortikoiddosis sollte 2 bis 3 Monate vor elektiven Eingriffen so niedrig wie möglich reduziert (in jedem Fall <10 mg/Tag), 1 bis 2 Wochen vor und am Operationstag jedoch stabil gehalten werden. csDMARDs können in vielen Fällen fortgeführt werden, Ausnahmen sind eine Reduktion hoher Methotrexat-Dosierungen auf ≤15 mg/Woche und Auswaschen des Leflunomid bei hohem Infektionsrisiko. Azathioprin, Mycophenolat und Ciclosporin sollten 1 bis 2 Tage vor der Operation pausiert werden. Unter bDMARDs können Operationen zum Ende des jeweiligen Therapieintervalls geplant werden. Januskinase(JAK)-Inhibitoren sollten bei größeren Eingriffen für 3 bis 4 Tage pausiert werden. Apremilast kann fortgeführt werden. Bei notwendiger Unterbrechung gilt für alle Substanzen, die Therapie in Abhängigkeit der Wundheilung baldmöglichst wieder zu beginnen.
Schlussfolgerungen: Ob bDMARDs das Infektionsrisiko perioperativ erhöhen und welche Rolle die Absetzzeit dabei spielt, bleibt bei gegenwärtiger Evidenz noch unklar. Um das Risiko eines Krankheitsschubs unter längerer Therapiepause zu minimieren, wurde in den aktualisierten Empfehlungen die perioperative Pausierung von bDMARDs von mindestens 2 Halbwertszeiten auf ein Therapieintervall reduziert.

Schlüsselwörter
Operation · Glukokortikoide · Disease-modifying antirheumatic drugs · Biologika · Infektionsrisiko