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Practice Guidelines

2022 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

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Objective: To develop updated American College of Rheumatology/American Association of Hip and Knee Surgeons guidelines for the perioperative management of disease-modifying medications for patients with rheumatic diseases, specifically those with inflammatory arthritis (IA) and those with systemic lupus erythematosus (SLE), undergoing elective total hip arthroplasty (THA) or elective total knee arthroplasty (TKA).

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Methods: We convened a panel of rheumatologists, orthopedic surgeons, and infectious disease specialists, updated the systematic literature review, and included currently available medications for the clinically relevant population, intervention, comparator, and outcomes (PICO) questions. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence and the strength of recommendations using a group consensus process.
Results: This guideline updates the 2017 recommendations for perioperative use of disease-modifying antirheumatic therapy, including traditional disease-modifying antirheumatic drugs, biologic agents, targeted synthetic small-molecule drugs, and glucocorticoids used for adults with rheumatic diseases, specifically for the treatment of patients with IA, including rheumatoid arthritis and spondyloarthritis, those with juvenile idiopathic arthritis, or those with SLE who are undergoing elective THA or TKA. It updates recommendations regarding when to continue, when to withhold, and when to restart these medications and the optimal perioperative dosing of glucocorticoids.
Conclusion: This updated guideline includes recently introduced immunosuppressive medications to help decision-making by clinicians and patients regarding perioperative disease-modifying medication management for patients with IA and SLE at the time of elective THA or TKA.
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Introduction

Advances in antirheumatic therapy have led to remarkable improvements in treatment and quality of life for people with rheumatic musculoskeletal diseases (RMDs); however, total hip arthroplasty (THA) and total knee arthroplasty (TKA) remain a mainstay of treatment among RMD patients with advanced symptomatic joint damage, most frequently those with inflammatory arthritis (IA), including spondylarthritis (SpA), rheumatoid arthritis (RA), or psoriatic arthritis (PsA), and those with systemic lupus erythematosus (SLE) [1–7]. THA and TKA are successful procedures that improve mobility and decrease pain for people with RMD and end-stage arthritis. However, the risk of superficial and deep periprosthetic joint infection (PJI), a devastating complication, is increased after surgery in people with RMD, and avoiding infection is a top priority for them: patients with RA have a 50% increased risk of PJI compared to those with osteoarthritis [8,9]. A panel of patients with RA was convened in 2017 prior to the publication of the American College of Rheumatology/American Association of Hip and Knee Surgeons (ACR/AAHKS) perioperative guideline and clearly stated that any risk of infection, while rare, was much more significant to them than the possibility of a postoperative flare, despite flares reported in >60% of patients after surgery [8,10–12]. Recommendations regarding perioperative management of antirheumatic medications in the 2017 ACR/AAHKS guideline need updating to include drugs introduced in the interim, as well as review of more recent relevant publications.

The optimal strategy for perioperative medication management remains unknown, but antirheumatic therapy is a readily modifiable risk factor for infection, whereas other risk factors for adverse outcomes, including disease activity or severity or long-term glucocorticoid (GC) use, may not be modifiable [13–15]. The ACR systematically updates guidelines every 5 years; therefore, to update the 2017 perioperative medication management guideline, the ACR and AAHKS convened a panel of rheumatologists, orthopedic surgeons, and infectious disease specialists and conducted a systematic review of the new literature published since the last guideline, adding new medications to those previously available, although direct applicable evidence remains sparse in the literature. This guideline applies to management of antirheumatic medication for adult patients with IA, including those with RA, SpA, PsA, or ankylosing spondylitis (AS), adults with juvenile idiopathic arthritis (JIA), and adult patients with SLE undergoing elective THA or TKA.

Given the increased infection risk seen in patients with IA and patients with SLE undergoing these procedures, the existing evidence base used to guide our recommendations, the time afforded by these elective procedures to manage medications, and the frequent use of these procedures in patients with IA or SLE [4,6,16], we have restricted our recommendations to those undergoing either THA or TKA. A guideline cannot address all clinical situations and scenarios but seeks to provide recommendations for commonly encountered clinical problems.

While the principles surrounding these recommendations may be extrapolated and applied to other surgical procedures, it should be noted that the evidence and consensus used to inform this guideline were drawn primarily from orthopedic literature. As in the prior version, this guideline does not address indications for THA or TKA, medical decisions unrelated to antirheumatic drug therapy, the choice of the implant, the surgical approach, or the perioperative evaluation and management of concurrent disease, such as that affecting the cervical spine of patients with RA. Although routine perioperative care and preoperative optimization for patients with RA, SpA, JIA, or SLE include assessing risk of venous thromboembolism and major acute coronary events [17,18], this guideline does not address cardiac risk assessment or perioperative venous thromboembolism prophylaxis, as both are covered in existing guidelines [19–22]. The goal of this updated guideline is to provide optimal support for clinicians and patients making decisions regarding medication management at the time of elective THA or TKA surgery.

Methods

This guideline was developed following the ACR guideline development process and in accordance with ACR policies guiding management of conflicts of interest and disclosures (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines), which includes Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology and a framework for developing and presenting evidence [23,24] and adheres to Appraisal of Guidelines for Research and Evaluation (AGREE) criteria [25]. The process for updating the 2017 guidelines began in 2021 [26]. The populations included in this guideline are defined in Table 1 and are unchanged. Table 2 contains a list of the included drugs, along with their dosing intervals (reflecting the duration of effect), with the drugs newly added for this 2022 update denoted with footnotes. Brand names were used for newer medications that are likely to be unfamiliar to some orthopedists. Supplementary Appendix 1, *Arthritis Care & Research*, includes a detailed description of the methods. Briefly, 3 teams were formed: a Core Leadership Team, a Literature Review Team, and a Voting Panel. The Core Leadership Team (SMG, BDS, AY, and JAS) confirmed that the population,

Table 1
Populations included in this guideline

Adults age ≥18 years diagnosed with RA, SpA, including AS and PsA, JIA, or SLE who are deemed to be appropriate surgical candidates, are undergoing elective THA or TKA, and who are receiving antirheumatic drug therapy at the time of surgery
All patients carrying the above diagnoses without restriction to those meeting classification criteria
SLE includes patients with severe or not severe SLE, defined as follows
Severe SLE: currently treated (induction or maintenance) for severe organ manifestations: lupus nephritis, CNS lupus, severe hemolytic anemia (hemoglobin <9.9 gm/dl), platelets <50,000, vasculitis (other than mild cutaneous vasculitis), including pulmonary hemorrhage, myocarditis, lupus pneumonitis, severe myositis (with muscle weakness, not just high enzymes), lupus enteritis (vasculitis), lupus pancreatitis, cholecystitis, lupus hepatitis, protein-losing enteropathy, malabsorption, orbital inflammation/myositis, severe keratitis, posterior severe uveitis/retinal vasculitis, severe scleritis, optic neuritis, anterior ischemic optic neuropathy (derived from the SELENA–SLEDAI flare index and the BILAG 2004 index)
Not severe SLE: not currently treated for above manifestations

RA = rheumatoid arthritis; SpA = spondyloarthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; THA = total hip arthroplasty; TKA = total knee arthroplasty; CNS = central nervous system; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; BILAG = British Isles Lupus Assessment Group.

intervention, comparator, and outcomes (PICO) questions would be the same as the ones used for the 2017 guideline, with updated medication lists to include any therapies approved for use in the US as of August 26, 2021, the stop date of our literature review (see Table 2 for medication list and Supplementary Appendix 2, *Arthritis Care & Research*, for the PICO list, including outcomes; see Supplementary Appendices 3 and 4 for the search strategies and study selection process, respectively).

The Literature Review Team performed updates of the systematic literature review for each PICO, graded the quality of evidence (high, moderate, low, very low), and produced the evidence report (see Supplementary Appendix 5, *Arthritis Care & Research*). The systematic literature review was updated by searching for relevant published literature from March 6, 2016, to August 26, 2021, because the previous systematic literature review for the 2017 guideline was performed from January 1, 1980, through March 6, 2016. Although the updated literature review added to the evidence report, the overall quality of the evidence remained low due to indirect evidence or small numbers of included cases. Because the overall quality of evidence was low, we included a review of the background risk for adverse events associated with THA or TKA in patients with RA, SpA, JIA, or SLE that is independent of use of the medications of interest to give context to our deliberations. Severe SLE is defined in Table 1 and refers to those patients with severe organ manifestations such as nephritis. We did not repeat our search for additional indirect evidence regarding medication risks associated with our drugs of interest; included medications are listed in Table 2.

The Voting Panel included 2 patients who have undergone arthroplasty surgery and who participated in the 2017 guideline's Patient Panel, one of whom participated in the previous Voting Panel. The panel reviewed evidence summaries from both the 2017 project and this update and discussed and voted on recommendation statements. The recommendation regarding anifrolumab and voclosporin was voted on via email. A recommendation could be either in favor of or against the proposed intervention and either strong or conditional. Consensus required ≥70% agreement on both direction (for or against) and strength (strong or conditional) for each recommendation. Per GRADE methodology, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is more sensitive to individual patient preferences, or when costs are expected to impact the decision. Thus, conditional recommendations refer to decisions in which incorporation of patient preferences is a particularly essential element of decision-making.

Rosters of the Core Leadership Team, Literature Review Team, and Voting Panel are included in Supplementary Appendix 6, *Arthritis Care & Research*. This study did not involve human subjects, and therefore, approval from Human Studies Committees was not required.

Results/Recommendations

How to interpret the recommendations

1. All recommendations in this guideline are conditional due to the quality of the evidence (see bolded statements in Table 3). A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients but may not apply to all patients. Because of this, conditional recommendations are preference sensitive and always warrant a shared decision-making approach. No strong recommendations are made in this guideline, although no recommendation achieved <80% of the vote, and 4 of the votes were unanimous.
2. For each recommendation, a summary of the supporting evidence or conditions is provided.
3. Therapies that were approved after the end of the original systematic literature review on March 6, 2016 through August 2021 are included in these updated recommendations. Therapies approved after the end of the updated systematic review (March 6, 2016 to August 26, 2021) are not included in these recommendations.
4. PICO questions were combined in the final recommendations for clarity.

Recommendations

For patients with RA, AS, PsA, JIA, or all SLE undergoing elective THA or TKA, continuing the usual dosing of the following disease-modifying antirheumatic drugs (DMARDs) through surgery is conditionally recommended: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and/or apremilast.

This conditional recommendation now includes apremilast, but it is otherwise unchanged from the 2017 guideline. Four observational studies provided additional indirect evidence to the previous systematic literature review and found no relationship between the included drugs and the risk of postoperative infections, although the number of included cases and events were low [11,27–29]. Patients with a history of severe or recurrent infections or prior prosthetic joint infection may elect to withhold these medications before surgery.

For patients with RA, AS, PsA, or JIA undergoing elective THA or TKA, withholding all biologics, including rituximab, prior to surgery

Table 2
Medications included in this 2022 guideline update[a]

	Dosing interval	Recommended timing of surgery since last medication dose
Medications to continue through surgery		
DMARDs: continue these medications through surgery (all patients)		
Methotrexate	Weekly	Anytime
Sulfasalazine	Once or twice daily	Anytime
Hydroxychloroquine	Once or twice daily	Anytime
Leflunomide (Arava)	Daily	Anytime
Doxycycline	Daily	Anytime
Apremilast (Otezla)	Twice daily[b]	Anytime[b]
Severe SLE-specific medications: continue these medications in the perioperative period in consultation with the treating rheumatologist[c]		
Mycophenolate mofetil	Twice daily	Anytime
Azathioprine	Daily or twice daily	Anytime
Cyclosporine	Twice daily	Anytime
Tacrolimus	Twice daily (IV and PO)	Anytime
Rituximab (Rituxan)	IV every 4–6 months[b]	Month 4–6[b]
Belimumab SC (Benlysta)	Weekly [b]	Anytime[b]
Belimumab IV (Benlysta)	Monthly [b]	Week 4[b]
Anifrolumab (Saphnelo)[d]	IV every 4 weeks[b]	Week 4[b]
Voclosporin (Lupkynis)[d]	Twice daily[b]	Continue[b]
Medications to withhold prior to surgery[e]		
Biologics: withhold these medications through surgery		
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Adalimumab (Humira)	Every 2 weeks	Week 3
Etanercept (Enbrel)	Every week	Week 2
Abatacept (Orencia)	Monthly (IV) or weekly (SC)	Week 5; week 2
Certolizumab (Cimzia)	Every 2 or 4 weeks	Week 3 or 5
Rituximab (Rituxan)	2 doses 2 weeks apart every 4–6 months	Month 7
Tocilizumab (Actemra)	Every week (SC) or every 4 weeks (IV)	Week 2; week 5
Anakinra (Kineret)	Daily	Day 2
IL-17 secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Ixekizumab (Taltz)[d]	Every 4 weeks[b]	Week 5[b]
IL-23 guselkumab (Tremfya)[d]	Every 8 weeks[b]	Week 9[b]
JAK inhibitors: withhold this medication 3 days prior to surgery[f]		
Tofacitinib (Xeljanz)	Daily or twice daily[b]	Day 4[b]
Baricitinib (Olumiant)[d]	Daily[b]	Day 4[b]
Upadacitinib (Rinvoq)[d]	Daily[b]	Day 4[b]
Not severe SLE: withhold these medications 1 week prior to surgery		
Mycophenolate mofetil	Twice daily	1 week after last dose[b]
Azathioprine	Daily or twice daily	1 week after last dose
Cyclosporine	Twice daily	1 week after last dose[b]
Tacrolimus	Twice daily (IV and PO)	1 week after last dose[b]
Rituximab (Rituxan)	Every 4–6 months	Month 7
Belimumab IV (Benlysta)	Monthly[b]	Week 5[b]
Belimumab SC (Benlysta)	Weekly[b]	Week 2[b]

DMARDs = disease-modifying antirheumatic drugs; SLE = systemic lupus erythematosus; IV = intravenous; PO = by mouth; SC = subcutaneous; IL = interleukin.
[a] Dosing intervals obtained from prescribing information provided online by pharmaceutical companies.
[b] Recommendation that has changed since 2017.
[c] Severe SLE indicates organ-threatening disease.
[d] Drug added for 2022 update.
[e] For patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or all SLE for whom antirheumatic therapy was withheld prior to undergoing total joint arthroplasty, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days.
[f] Recommendation pertains to infection risk and does not account for risk of cardiac events or venous thromboembolism.
Adapted from the 2017 American College of Rheumatology/American Association of Hip and Knee Surgeons guideline (26).

and planning the surgery after the next dose is due is conditionally recommended.

This recommendation no longer includes patients with SLE, who are addressed separately (see below for rationale) but has not otherwise changed. Table 2 contains the included medications.

This recommendation is conditional because the evidence is indirect and there is a lack of a comparator group in the included studies [27,30]. This recommendation was informed by additional new evidence from 2 studies that used administrative claims data to accurately capture the timing of infliximab or abatacept use before THA or TKA and to evaluate associations between biologics timing and outcomes [30,31]. In both studies, there was no difference in postoperative outcomes when comparing short medication interruptions of ~1 dosing interval to longer interruptions. Results were similar in an additional study evaluating infliximab or abatacept timing before other types of surgery [32]. These studies also showed no difference in outcomes in patients receiving infliximab or abatacept within 1 dosing interval before surgery, although patients receiving intravenous abatacept within 2 weeks of surgery (one-half of a dosing interval) had a numerically higher rate of adverse events that was not statistically significant [31].

Table 3
Recommendations for perioperative management of antirheumatic drug therapy in patients with inflammatory arthritis and those with systemic lupus erythematosus (SLE) undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA)

Recommendation/strength of recommendation	Level of evidence
For patients with RA, AS, PsA, JIA, or all SLE undergoing THA or TKA, continuing the usual dosing of the following DMARDs through surgery is **conditionally** recommended: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, and/or apremilast.[a]	Low to moderate
For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding all biologics, including rituximab, prior to surgery and planning the surgery after the next dose is due is **conditionally** recommended.	Low
For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding tofacitinib, baricitinib, and upadacitinib for at least 3 days prior to surgery is **conditionally** recommended.[b]	Low
For patients with SLE (not severe) undergoing THA or TKA, withholding the current dose of mycophenolate mofetil, mycophenolic acid, azathioprine, cyclosporine, mizoribine, or tacrolimus 1 week prior to surgery is **conditionally** recommended.	Low
For patients with SLE (not severe) undergoing THA or TKA, withholding the usual dose of belimumab and rituximab prior to surgery is **conditionally** recommended.	Low
For patients with severe SLE who have been deemed appropriate to undergo THA or TKA, continuing the usual dose of mycophenolate mofetil, mycophenolic acid (Myfortic), azathioprine, mizoribine, cyclosporine, or tacrolimus, anifrolumab, and voclosporin through surgery is **conditionally** recommended.[b]	Low
For patients with severe SLE undergoing THA or TKA, continuing belimumab and planning surgery in the last month of the dosing cycle of rituximab is **conditionally** recommended.[b]	Low
For patients with RA, AS, PsA, or all SLE for whom antirheumatic therapy was withheld prior to undergoing TJA, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days, is **conditionally** recommended.	Low
For patients with RA, AS, PsA, or all SLE undergoing THA or TKA who are receiving glucocorticoids for their rheumatic condition, continuing their current daily dose of glucocorticoids rather than administering supraphysiologic doses of glucocorticoids on the day of surgery is **conditionally** recommended.	Low

RA = rheumatoid arthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; DMARDs = disease-modifying antirheumatic drugs; TJA = total joint arthroplasty.
[a] Apremilast is a change from the prior recommendation.
[b] Indicates a change from the prior recommendation.

Planning the surgery after the end of the dose interval was favored because active drug levels would be low. For example, for rituximab, dosed every 6 months, surgery should be planned during month 7, and for adalimumab, dosed every 2 weeks, surgery should be planned for week 3 (see Table 2 for drug dosing intervals). Patients and their physicians might elect surgery within the dosing cycle if their symptoms from the operative joint are severe and the anticipated pain relief provided by surgery outweighs the possible risk of infection as may occur with advanced osteonecrosis. In addition, those patients whose disease has been challenging to control may also elect to continue their medications rather than risk loss of disease control, as this may occur when medications are withheld.

For patients with RA, AS, PsA, or JIA undergoing THA or TKA, withholding tofacitinib, baricitinib, and upadacitinib for at least 3 days prior to surgery is conditionally recommended.

This conditional recommendation was changed from the prior guideline. For the previous guideline, while the short serum half-life of tofacitinib was known, concern for a longer duration of the immune effect prompted the recommendation to withhold tofacitinib for 7 days prior to surgery. The new recommendation was informed by trial data demonstrating rapid increases in disease activity after interrupting tofacitinib therapy, suggesting a rapid reversal of the immunosuppressive effects, so the recommendation was changed to withhold tofacitinib for 3 days prior to surgery [33]. The serum half-life of the newer JAK inhibitors is similar to that of tofacitinib. However, patients and their physicians might withhold JAK inhibitors for a longer period if a patient has a history of infections or a prior prosthetic joint infection. This recommendation does not pertain to the risk of a cardiac event or a venous thromboembolic event (VTE) potentially associated with JAK inhibitors.

For patients with SLE (not severe) undergoing THA or TKA, withholding the current dose of mycophenolate mofetil, mycophenolic acid, azathioprine, cyclosporine, mizoribine, or tacrolimus 1 week prior to surgery is conditionally recommended.

This recommendation remains unchanged from the prior guideline. Patients with frequent flares or SLE that is difficult to control might continue their medications, but the majority could be followed closely after surgery to address a flare.

For patients with SLE (not severe) undergoing THA or TKA, withholding the usual dose of belimumab and rituximab prior to surgery is conditionally recommended.

This recommendation is unchanged from the prior guideline. Patients with SLE that is not severe would not be at risk for permanent organ damage should they flare. In addition, nonsevere SLE patients could be followed up closely after surgery, and an intervention could be made to treat a flare as needed. Patients with frequent flares or SLE that is difficult to control might choose to continue their medications in a shared decision-making approach with their physicians, but the majority could be followed up closely after surgery to address a flare.

For patients with severe SLE (Table 1) who have been deemed appropriate to undergo THA or TKA, continuing the usual dose of mycophenolate mofetil, mycophenolic acid (Myfortic), azathioprine, mizoribine, cyclosporine, or tacrolimus, anifrolumab, and voclosporin through surgery is conditionally recommended.

This recommendation has changed with the addition of anifrolumab and voclosporin, recently introduced medications for severe SLE. These medications should be continued through surgery. There were no new data available to update this recommendation, so the guidance reflects the concern about disease flares and the risk of organ damage in severe SLE that could be precipitated by medication withdrawal; although postoperative adverse events are linked to disease severity, they have not been clearly associated with medication use. As noted in the previous guideline, the patient's rheumatologist should be consulted regarding medication management. A patient with severe SLE who has been stable for >6 months or who has a history of recurrent or severe infections might discontinue the medications in the perioperative period.

For patients with severe SLE undergoing THA or TKA, continuing belimumab and planning surgery in the last month of the dosing cycle of rituximab is conditionally recommended.

In the prior guideline, rituximab was included in the recommendations with other biologics, but increased use for SLE treatment, the long dosing interval for rituximab, and the indication of

belimumab as therapy for severe SLE manifestations has informed this change. Surgery should be planned at the end of the dosing cycle, typically during month 5 or 6 for patients receiving rituximab every 6 months, and to avoid disruptions of therapy rather than wait longer, given the long dosing interval for rituximab. The panel noted that rituximab is used in SLE without an indication approved by the US Food and Drug Administration (FDA) but also noted that it has been included in SLE treatment guidelines [34]. In addition, there is a risk of disease flares in patients with severe SLE with organ damage if therapy is interrupted. Situations such as prior severe infections and/or SLE that has been stable for >6 months might prompt the clinician to withhold rituximab for a longer period. Recent studies describe an increased risk of adverse events associated with SLE that appears to be more significant for THA than TKA, but there are no strong data to suggest that these outcomes are related to medication management [34–37].

This recommendation has changed since the prior guideline in part because of the additional indication for the use of belimumab in severe SLE including nephritis, as well as increased comfort with belimumab among clinicians and patients given its widespread use, low infection risk described in clinical trials, and inclusion in SLE treatment guidelines [34,38,39]. The panel remained concerned about disruptions of successful treatment regimens in patients with severe SLE given the potential for severe organ damage, although belimumab might be withheld in stable patients with a history of prior infections.

For patients with RA, AS, PsA, or all SLE for whom antirheumatic therapy was withheld prior to undergoing total joint arthroplasty, antirheumatic therapy should be restarted once the wound shows evidence of healing, any sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no ongoing nonsurgical site infection, which is typically ~14 days after surgery, is conditionally recommended.

Drugs should be restarted based on the clinical status of the patient and the status of the healing wound. Although there was additional evidence to support this recommendation from the literature review, it was indirect and of very low quality across the critical outcomes. Patients with nonrheumatic diseases were included, or the study did not include a comparator group. In one study using a large Medicare data set, outcomes were better in patients who restarted infliximab within 4 weeks after surgery compared to those who restarted later, but the authors noted that this was likely because postoperative complications led to delays in restarting therapy [30].

Patients and their physicians might elect longer periods of not taking medication given a history of prior severe infections or a history of a prior prosthetic joint infection.

For patients with RA, AS, PsA, or all SLE undergoing THA or TKA who are receiving GCs for their rheumatic condition, continuing their current daily dose of GCs rather than administering supraphysiologic doses of GCs on the day of surgery is conditionally recommended.

This recommendation is unchanged from the previous guideline, with 2 new studies considered. One study found no significant association of supraphysiologic ("stress dose") GC doses with adverse events in SLE patients undergoing THA or TKA, but the sizes of the patient groups were small [35]. Another study of 432 patients with RA who underwent THA and TKA concluded that patients with higher GC exposure were more likely to have hyperglycemia and other complications and that the risk of short-term complications is increased by 8.4% for every 10-mg increase in GC dose, and a lower cumulative GC dose was not associated with hypotension [40]. Exceptions to this recommendation are unchanged. However, wound healing may be affected by use of low-dose (<5 mg/day) GCs when the cumulative dose is high, which may also contribute to perioperative infection risk. This recommendation does not refer to patients with JIA who may have received GCs during childhood developmental stages or to patients receiving GCs to treat primary adrenal insufficiency or primary hypothalamic disease, all of whom may require supraphysiologic doses of GCs to maintain hemodynamic stability.

Discussion

We have updated the 2017 ACR/AAHKS guideline for the perioperative management of DMARDs, biologics, and GCs for adult patients with RA, SpA including AS and PsA, JIA, and SLE undergoing elective THA or TKA. This guideline is intended for use by clinicians and patients and balances the risk of flares of disease when medications are withheld versus infection risk attributed to the medications when they are continued. This update adds new medications introduced and reviews the studies published since the 2017 ACR/AAHKS guideline that have informed our recommendations. The scope of the guideline has not changed and addresses when to withhold and when to restart disease-modifying therapies, as well as perioperative GC management. Although we included patients in our Voting Panel, we did not reinstate the Patient Panel due to the risk associated with the COVID-19 pandemic, and because we thought it was unlikely that patients' priorities regarding the risk of flare versus the risk of infection would have changed. The updated medication list includes medications introduced to treat RA and SpA, including AS and PsA. We have included perioperative management recommendations for the recently introduced JAK-targeted therapies, baricitinib and upadacitinib, in addition to tofacitinib. We have included new management recommendations for the interleukin-17 (IL-17) blocking agent, ixekizumab, the IL-23–blocking drug guselkumab, and the novel synthetic DMARD apremilast. Anifrolumab, approved by the FDA on July 30, 2021, and voclosporin, approved January 22, 2021, were included in this guideline, although there is no information regarding their use in the perioperative period. They increase the risk of infection, and therefore the use of these medications in patients with severe SLE would merit review by the treating rheumatologist in consideration of surgery. The Voting Panel agreed with their inclusion via email voting.

This guideline is informed by cohort studies including pharmacoepidemiologic studies using large administrative databases. To our knowledge, there have been no randomized controlled trials since the publication of the prior ACR/AAHKS guideline in 2017, so much of the data supporting these recommendations remains largely indirect or of low quality. Similar to the last guideline, the major limitation remains the paucity of high-quality direct evidence regarding the added risk of infection from medication use at the time of THA or TKA; therefore, these recommendations continue to rely on indirect studies describing results in patients without rheumatic diseases or on assumptions or conclusions extrapolated from nonsurgical studies. An additional limitation of this guideline is the lack of participation from other orthopedic surgical specialties such as spine or foot and ankle. Moreover, our literature review focused only on THA and TKA, so concerns of other surgical specialists may have not been addressed by our focused assessment of THA and TKA. Therefore, we are unable to generalize our recommendations to rheumatic disease patients undergoing other orthopedic surgical procedures, as well as non-orthopedic surgery. However, the principles underlying our recommendations may provide a framework to apply in other surgical settings.

A strength of this guideline is the robust collaboration between orthopedic hip and knee surgeons and rheumatologists, as well as the inclusion of patients, epidemiologists, and specialists in infectious diseases who represent other stakeholders for this project.

This multidisciplinary collaboration facilitated the uptake and dissemination of the prior guideline, and it is anticipated that these recommendations will be similarly distributed and used to guide busy clinicians and their patients at the time of THA and TKA. GRADE methodology supports consensus-based recommendations that can be reached based on low-quality evidence across the critical outcomes and transparently rates the strength of the recommendation as well as the quality of the evidence supporting the recommendation [24,41]. Because most of the evidence informing this guideline is indirect and/or of low quality, all of the recommendations are conditional. Nonetheless, consensus of the Voting Panel was high. Four recommendations received 100% agreement, and none achieved <80% agreement.

This guideline does not address perioperative prophylaxis or treatment of VTEs or perioperative cardiac assessment, as these are addressed in several other focused publications. JAK inhibitors as a class carry an increased risk of VTE, which is a black box warning from the FDA, which more recently issued a warning regarding increased cardiovascular risk [42]. Future research should address an assessment of the perioperative cardiac and VTE risks associated with JAK inhibitors and other factors such as disease activity for which there is no direct evidence.

Perioperative management of rituximab has been a challenge given the long dosing interval of 6 months and the recognized risk of severe infection linked to its use [43–46]. In this updated guideline, we have separated the perioperative use of rituximab in SLE from the perioperative management of rituximab in other diseases [46]. Although rituximab has an FDA indication for RA, but not for SLE, the 2019 European Alliance of Associations for Rheumatology recommendations for the management of SLE include use of rituximab, providing an additional rationale for our change to separate the recommendations for RA and other rheumatic conditions from those for severe SLE [34]. Our recommendations are linked to drug dosing intervals given our assumption that the dosing interval reflects the period of immunosuppression; however, infection risk in patients treated with rituximab may be unrelated to the rituximab dosing interval and is increased in those with hypogammaglobulinemia [47,48]. Additional research is needed to increase understanding of the factors contributing to infection risk with rituximab therapy, such as duration of therapy or immunoglobulin levels at the time of surgery.

As previously, the recommendations that form this guideline are not treatment mandates. These recommendations will provide the backbone for a shared decision-making process between patient and physician regarding perioperative medication management around the time of surgery. The previous Patient Panel provided critical insight into the priorities of patients around the time of THA and TKA and the importance of open discussion and consultation between the perioperative physician, the orthopedic surgeon, and the rheumatologist. One patient representative on the current Voting Panel noted the anxiety that patients experience around changes to their medication regimens and urged clinicians to be cognizant of this important issue. Although not all scenarios can be addressed in the scope of a document such as this guideline, the most common scenarios are included, and these recommendations should supplement the usual perioperative clinical assessment, risk benefit discussions, and management for clinical optimization prior to surgery.

We continue to support ongoing research to better inform perioperative management of medications used commonly in rheumatic diseases. While we have added to our information base regarding GC management and the timing of biologic infusion therapy, we still lack high-level data from randomized controlled trials to provide clearer answers to the important questions addressed in the guideline. Data concerning traditional synthetic DMARDs should be updated with randomized controlled trials, and data regarding perioperative management of biologics also needs more definitive study. Patients with rheumatic diseases have higher rates of concomitant metabolic syndrome and cardiac disease and may also be at potentially higher risk of perioperative cardiac and/or thromboembolic events. Therefore, consideration of the role of comorbidities and the interaction with antirheumatic therapy should also be pursued.

In summary, this guideline provides an update to the ACR/AAHKS 2017 guideline to provide clinicians and patients information about risks and benefits regarding management of perioperative antirheumatic medication to inform decisions prior to THA and TKA. We have updated our evidence base through our search of the current literature and assessed that information through the lens of our clinical expertise and the perspectives of the patients who have participated in this process. We acknowledge the gaps in our information base and intend to continue to fill those gaps as more research is available.

Author Contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Goodman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design. Goodman, Springer, Klatt, Russell, Sah, Abdel, Johnson, Turner, Yates, Singh. Acquisition of data. Goodman, Springer, George, Klatt, MacKenzie, Sah, Abdel, Johnson, Mandl, Sculco, Turgunbaev, Yates, Singh. Analysis and interpretation of data. Goodman, Springer, Chen, Davis, Fernandez, Figgie, Finlayson, George, Giles, Gilliland, Klatt, MacKenzie, Michaud, Miller, Russell, Sah, Abdel, Johnson, Turgunbaev, Yates, Singh.

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