

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

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Objective. This collaboration between the American College of Rheumatology and the American Association of Hip and Knee Surgeons developed an evidence-based guideline for the perioperative management of antirheumatic drug therapy for adults with rheumatoid arthritis (RA), spondyloarthritis (SpA) including ankylosing spondylitis and psoriatic arthritis, juvenile idiopathic arthritis (JIA), or systemic lupus erythematosus (SLE) undergoing elective total hip (THA) or total knee arthroplasty (TKA).

Methods. A panel of rheumatologists, orthopedic surgeons specializing in hip and knee arthroplasty, and methodologists was convened to construct the key clinical questions to be answered in the guideline. A multi-step systematic literature review was then conducted, from which evidence was synthesized for continuing versus withholding antirheumatic drug therapy and for optimal glucocorticoid management in the perioperative period. A Patient Panel was convened to determine patient values and preferences, and the Grading of Recommendations Assessment, Development and Evaluation methodology was used to rate the quality of evidence and the strength of recommendations, using a group consensus process through a convened Voting Panel of rheumatologists and orthopedic surgeons. The strength of the recommendation reflects the degree of certainty that benefits outweigh harms of the intervention, or vice versa, considering the quality of available evidence and the variability in patient values and preferences.

Results. The guideline addresses the perioperative use of antirheumatic drug therapy including traditional disease-modifying antirheumatic drugs, biologic agents, tofacitinib, and glucocorticoids in adults with RA, SpA, JIA, or SLE who are undergoing elective THA or TKA. It provides recommendations regarding when to continue, when to withhold, and when to restart these medications, and the optimal perioperative dosing of glucocorticoids. The guideline includes 7 recommendations, all of which are conditional and based on low- or moderate-quality evidence.

Conclusion. This guideline should help decision-making by clinicians and patients regarding perioperative antirheumatic medication management at the time of elective THA or TKA. These conditional recommendations reflect the paucity of high-quality direct randomized controlled trial data.

INTRODUCTION

Although the wide utilization of disease-modifying antirheumatic drugs (DMARDs) and biologic agents has improved the quality of life for patients with rheumatoid arthritis (RA), spondyloarthritis (SpA), juvenile idiopathic arthritis (JIA), or systemic lupus erythematosus (SLE), rates of total hip arthroplasty (THA) and total knee arthroplasty (TKA) remain high (1–6). Patients with rheumatic conditions report significant improvement in pain and function after THA or TKA, yet critical outcomes such as infection, dislocation, and readmission are reported to be higher for patients with RA, SpA, or SLE (7–10) compared to patients with osteoarthritis. At the time of arthroplasty in a high-volume orthopedic hospital, 46% of RA patients were receiving biologic agents, 67% were receiving nonbiologic DMARDs, and 25% were receiving glucocorticosteroids, while 75% of patients with SLE

were receiving immunosuppressive medications, and 15% were receiving glucocorticosteroids. The optimal strategy to manage these medications is not known (11–14). Inherent risk factors for infection, such as overall disability and disease activity/severity, may not be modifiable, but the optimal perioperative management of immunosuppressant therapy around the time of arthroplasty may present an opportunity to mitigate risk (15–19).

In this setting, clinicians require guidance regarding perioperative management of antirheumatic drug therapy. Direct evidence, however, which addresses perioperative management is sparse (20,21). To our knowledge, there are no randomized controlled trials (RCTs) evaluating the cessation and reintroduction of biologic agents at the time of THA or TKA. The relevant outcomes considered for these guidelines are the potential increase in infection risk added by the medications versus the risk of disease

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Significance & Innovations

- Patients with rheumatic diseases undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) are at increased risk for peri-prosthetic joint infection.
- Appropriate management of antirheumatic medication in the perioperative period may provide an important opportunity to mitigate risk.
- Nonbiologic disease-modifying antirheumatic drugs may be continued throughout the perioperative period in patients with rheumatic diseases who are undergoing elective THA and TKA.
- Biologic medications should be withheld as close to 1 dosing cycle as scheduling permits prior to elective THA and TKA and restarted after evidence of wound healing, typically 14 days, for all patients with rheumatic diseases.

flare when the medications are withheld. This guideline pertains only to adult patients with RA, SpA including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), JIA, or SLE, who are undergoing elective THA or TKA, and incorporates patient preferences.

This guideline addresses management of antirheumatic medication in those adult patients with diagnoses of RA, SpA, JIA, or SLE, but is not limited to those who meet classification criteria. This guideline is to be used for those who have elected and have been deemed appropriate candidates for THA or TKA. We would caution against extrapolation of this guideline to other orthopedic procedures until further data are available.

This guideline is intended for use by clinicians, including orthopedists, rheumatologists, and other physicians

performing perioperative risk assessment and evaluation, as well as patients. The guideline addresses common clinical situations, but may not apply in all exceptional or unusual situations. It is imperative that open and informed communication between the patient, orthopedic surgeon, and rheumatologist takes place. In addition, while cost is a relevant factor in health care decisions, it was not considered in this project.

The populations included in this guideline are shown in Table 1 (22–24). Figure 1 contains a list of the drugs included in the evaluation, along with their dosing intervals, as the Panel determined that the dosing interval and route were more relevant for this guideline because they reflect the duration of effect.

This guideline does not address indications for THA or TKA, medical decisions unrelated to antirheumatic drug therapy, choice of implant, surgical approach, or perioperative evaluation and management of concurrent disease, such as that affecting the cervical spine of patients with RA. Although patients with RA, SpA, JIA, or SLE should be assessed for risk of venous thromboembolism and major acute coronary event (8,25), this guideline does not address cardiac risk assessment or perioperative venous thromboembolism prophylaxis; both are covered in existing guidelines (26–29).

METHODS

Overall methodology. This guideline follows the American College of Rheumatology (ACR) guideline development process (<http://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines>), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of the available evidence and to develop the recommendations (30). Conflicts of interest and disclosures were

Table 1. Populations included in the guideline*

<p>Populations†</p> <p>Adults age ≥ 18 years diagnosed with rheumatoid arthritis, spondyloarthritis including ankylosing spondylitis and psoriatic arthritis, juvenile idiopathic arthritis, or SLE (see below), who are deemed to be appropriate surgical candidates, undergoing elective total hip arthroplasty or total knee arthroplasty, and who are treated with antirheumatic drug therapy at the time of surgery.</p> <p>SLE</p> <p>SLE includes patients with severe or not severe SLE (defined below), and who are in optimal condition for surgery:</p> <p>Severe SLE</p> <p>Currently treated (induction or maintenance) for severe organ manifestations: lupus nephritis, central nervous system lupus, severe hemolytic anemia (hemoglobin < 9.9), platelets $< 50,000/\text{ml}$, 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 BILAG 2004) (22–24).</p> <p>Not severe SLE</p> <p>Not currently treated for manifestations listed under Severe SLE.</p>
<p>* SLE = systemic lupus erythematosus; 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. † All patients carrying the diagnoses listed, without restriction to those meeting classification criteria.</p>

DMARDs: CONTINUE these medications through surgery.	Dosing Interval	Continue/Withhold
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	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 (Humira)	Weekly or every 2 weeks	Week 2 or 3
Etanercept (Enbrel)	Weekly or twice weekly	Week 2
Golimumab (Simponi)	Every 4 weeks (SQ) or every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade)	Every 4, 6, or 8 weeks	Week 5, 7, or 9
Abatacept (Orencia)	Monthly (IV) or weekly (SQ)	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 (SQ) or every 4 weeks (IV)	Week 2 Week 5
Anakinra (Kineret)	Daily	Day 2
Secukinumab (Cosentyx)	Every 4 weeks	Week 5
Ustekinumab (Stelara)	Every 12 weeks	Week 13
Belimumab (Benlysta)	Every 4 weeks	Week 5
Tofacitinib (Xeljanz): 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

Figure 1. Medications included in the 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. Dosing intervals were obtained from prescribing information provided online by pharmaceutical companies. DMARDs = disease-modifying antirheumatic drugs; SQ = subcutaneous; IV = intravenous; SLE = systemic lupus erythematosus; PO = oral.

managed according to ACR policy (available at www.rheumatology.org/Portals/0/Files/Perioperative-Management-Guidelines-Disclosure-Summary.pdf). The full methods are presented in Supplementary Appendix 1 (available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract>).

Using GRADE, a recommendation can be either in favor of or against the proposed intervention and either strong or conditional (31,32). Much of the evidence was indirect, coming from nonsurgical studies, and all evidence was low to moderate quality (33,34). A strong recommendation indicates that most or almost all informed patients would choose the recommended action. Conditional recommendations are those in which the majority of the informed patients would choose to follow the recommended course of action, but a minority might not (35,36).

Teams involved. This project was a collaboration between the ACR and the American Association of Hip and Knee Surgeons (AAHKS). All participating teams contained representatives from both organizations, including a Core Leadership Team for project oversight (5 members), the Literature Review Team, who reviewed the literature and compiled the literature report, the Expert Panel, who helped frame the scope of the project, and the Voting Panel (consisting of orthopedic surgeons, rheumatologists, an infectious disease expert, an SLE expert, patient representatives, rheumatology methodologists, and a GRADE expert), who determined the final recommendations (for a complete listing of Panel and Team members see Supplementary Appendix 2 [available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract>]). Additionally, a Patient Panel consisting of 11 adults with RA or JIA, all of whom had undergone THA or TKA, reviewed the evidence and provided input on their values and preferences.

PICO (population/intervention/comparator/outcomes) question development and importance of outcomes. The Core Leadership Team initially drafted the project scope, key principles, and relevant clinical PICO questions, which were then presented to the Expert Panel, the Voting Panel, and the Literature Review Team for their review at a face-to-face meeting where the project plan was defined. The relevant topics addressed included: 1) Should anti-rheumatic medications be withheld prior to elective THA/TKA? 2) If they are withheld, when should they be stopped? 3) If withheld, when should they be restarted after surgery? 4) In patients receiving glucocorticoids, what dose should be administered at the time of surgery? The full list of PICO questions is shown in Supplementary Appendix 3 (<http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract>).

Direct high-quality RCT data available comparing the risk of THA or TKA in those receiving versus not receiving the medications of interest, or comparing the background risk of THA and TKA in the populations of interest, were sparse. To address this gap, 2 questions were included to inform the recommendations. The first asked, "What is the background risk for serious adverse events including infections, or hospitalization, associated with use of each

of the candidate drugs in patients not undergoing surgery?" The second question asked, "What is the background risk of adverse events associated with THA or TKA, independent of use of candidate medications in the populations of interest?" The group determined that both superficial and deep surgical site infection (reported within the first year after surgery), non-surgical site infection (within 90 days of surgery), and disease flare were the most critical outcomes; other outcomes such as hospital readmission, death, and long-term arthroplasty outcome were also deemed relevant.

Systematic synthesis of the literature and evidence processing. Systematic literature searches were performed in Embase (searched since 1974), the Cochrane Library, and PubMed (searched since the mid-1960s) from January 1, 1980 through March 6, 2016. The search strategies were developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for PubMed and Cochrane Library and Emtree terms for Embase (see Supplementary Appendix 4, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract>). Text words were used in PubMed and Embase, and keyword/title/abstract words in the Cochrane Library. Searches resulted in 2,230 total references (see Supplementary Appendix 5, <http://onlinelibrary.wiley.com/doi/10.1002/acr.23274/abstract>). A final search update was performed for the time period of January 1 to September 8, 2016, using the inclusive search terms of the disease states, coupled separately with "arthroplasty"; no randomized trials were identified that were relevant to the guideline. DistillerSR software (<http://systematic-review.net/>) was used to screen the literature search results grouped by their match with the pertinent PICO questions.

The Literature Review Team analyzed and synthesized data from eligible studies. Due to the lack of RCTs, we were unable to prepare GRADE Summary of Findings tables for most PICO questions. Microsoft Excel was used for abstracting data from observational studies. When available, the evidence summaries included the benefits and harms for outcomes of interest across studies, the relative effect (with 95% confidence interval [95% CI]), the number of participants, and the absolute effects. We rated the quality of evidence for each critical and important outcome as high, moderate, low, or very low quality, taking into account limitations of study design (including the risk of bias), inconsistency, indirectness, imprecision, and other considerations (including publication bias).

Moving from evidence to recommendations. The Patient Panel attached far greater importance to infection at the time of surgery than to flares. They were unable to precisely quantify the difference in value, noting that it was greater than 10:1.

The Voting Panel met to decide the final recommendations. The Panel discussed the evidence in the context of both their clinical experience and the input from the Patient Panel. The Panel voted anonymously, and 80% agreement defined the threshold for a recommendation; if 80% agreement was not achieved during an initial vote,

the Panel members held additional discussions before revoting. Considerations that led to rating down of quality of evidence included indirectness (much of the evidence came from RCTs outside of the surgical context, or from foot or spine procedures in which infection risks may vary markedly from THA or TKA); heterogeneity in baseline medication dose and duration, particularly relevant in studies addressing glucocorticoid “stress-dose” therapy; and imprecision associated with small sample size.

All recommendations were supported by more than 80% of the Panel, and all but 1 were supported unanimously. In some instances, the Panel combined PICO questions into 1 final recommendation. For recommendations to withhold a medication, a recommendation for the suggested timing of surgery in relation to the last drug-dose was included.

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 2). 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.
2. For each recommendation, a summary of the supporting evidence or conditions is provided.
3. Therapies that were approved after the original systematic literature review are not included in these recommendations.
4. PICO questions were combined in the final recommendations for clarity.

Recommendations

1. RA, SpA including AS and PsA, JIA, and SLE receiving nonbiologic DMARDs

Continue the current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine for patients undergoing elective THA or TKA (Table 2).

This conditional recommendation was based on low- to moderate-quality evidence. A systematic review of literature, which included RCTs of continuing versus discontinuing DMARDs at the time of surgery, revealed that the risk of infections was in fact decreased, with continuing DMARDs having a relative risk (RR) of 0.39 (95% CI 0.17–0.91) (37,38). The evidence base is rated down from high to moderate for reduction in infection risk after orthopedic surgery when these drugs are continued, because of risk of bias. There is indirect evidence describing a low infection risk with these specific DMARDs in settings other than THA and TKA (39). This recommendation was based on infection risk, although flares are also less frequent after surgery in those who continue

DMARDs, and the RRs of flares when DMARDs are continued versus stopped (RR 0.06 [95% CI 0.0–1.10]) were derived from low-quality evidence (37,40).

2. RA, SpA including AS and PsA, JIA, or SLE

Withhold all current biologic agents prior to surgery in patients undergoing elective THA or TKA, and plan the surgery at the end of the dosing cycle for that specific medication (Table 2).

This recommendation was based on evidence that was rated down in quality for indirectness, as no RCTs were performed in patients undergoing THA or TKA. We abstracted data from a systematic review of literature that included systematic reviews and meta-analyses of biologic agents versus placebo (and occasionally versus control treatment including nonbiologic DMARDs) in nonsurgical patients, which revealed that the risk of serious infections was increased with biologic agents, with most odds/hazards/risk ratios ~1.5 (range 0.61–8.87) and a higher risk of serious adverse events with most odds/hazards/risk ratios ~1.5 (range 0.33–2.54) (41–87). Our systematic review did not provide ample evidence that would support a differential risk of serious infection among available biologic agents (41–87). Because avoiding infection was significantly more important to patients than flares in the postoperative period, the Panel did not support separating biologic agents regarding infection risk in the perioperative period until further studies clarify and establish differences in risk (41–87). The literature review also revealed that the risk of postoperative infection complications after total joint arthroplasty (TJA) was increased in patients with RA nearly 2-fold, and deep infection complications increased by 1.5-fold (2,56); in SLE, overall postoperative complications were increased 1.3-fold, and septicemia by 2-fold (8), although medication use at the time of surgery was not always reported. In addition, a systematic review, meta-analysis, and network meta-analysis revealed that infection risk for biologic agents is strongly associated with high-dose therapy (higher dose than the standard) and may not be associated with low-dose biologic agents (42), so serum half-life may not correspond to the duration of the immunosuppressant effect. The dosing cycle was therefore chosen as more relevant in determining the withholding interval (88–91) and timing the surgery at the end of the dosing interval at the nadir of the drug effect.

With regard to patients with SLE, a systematic review of literature that included systematic reviews and meta-analyses of rituximab versus placebo (and occasionally versus control treatment including nonbiologic DMARDs) in nonsurgical patients with RA and SLE revealed the risk of serious infections with rituximab with a range of RRs from 0.66 to 0.73 (41,45), and a risk for all serious adverse events with a range of RRs from 0.85 (95% CI 0.62–1.17) to 0.89 (95% CI 0.7–1.14) (59,92). However, most data were indirect and the Panel considered these medications to be similar to tumor necrosis factor inhibitors used for the treatment of RA, which usually have a risk of infection. Moreover, rituximab is not approved by the US Food and Drug Administration (FDA) for treatment of SLE, and belimumab, although FDA-approved for use in SLE, has not been studied in manifestations of severe SLE (e.g.,

lupus nephritis), so the Panel recommended withholding these medications prior to surgery and planning the surgery for the end of the dosing cycle, due to the risk of infection and the paucity of data supporting perioperative benefit in SLE (93–95).

Observational studies reveal that patients with severe or active SLE have a higher risk of adverse events after surgery, but there is no approved role for these biologic agents for patients with severe SLE, including perioperative risk mitigation. SLE manifestations of rash and synovitis are the common clinical indications for belimumab (95,96), and are not thought to increase perioperative risk. There is no direct evidence, however, linking perioperative infection risk to the use of these biologic agents, and little is known about the association of surgical risk with biologic agents for patients with SLE. Since the duration of the immunologic effects of these drugs does not correspond to the serum level, the Panel based the recommendation on the dosing interval (88–91). The Patient Panel did not include patients with SLE, and they were reluctant to vote on SLE medication management strategies because they were uncertain about the value SLE patients would place on flares, which might be organ-threatening, compared to infection risk.

As an example, using this guideline, patients treated with adalimumab, routinely dosed at 2-week intervals, would plan their surgery in week 3, while patients treated with infliximab, when dosed every 8 weeks, would schedule their surgery in the week after the first withheld dose during week 9. Patients treated with rituximab every 6 months would schedule their surgery, when possible, at the week after the first withheld dose during month 7. Patients with SLE receiving belimumab, which is given every 4 weeks, would schedule their surgery during week 5.

3. RA, SpA including AS and PsA, or JIA

Withhold tofacitinib for at least 7 days prior to surgery in patients with RA, SpA including AS and PsA, or JIA undergoing THA or TKA (Table 2).

This recommendation was based on indirect evidence from systematic reviews and meta-analyses of tofacitinib versus placebo (and occasionally versus control treatment including nonbiologic DMARDs) in nonsurgical patients showing that the risk of serious infections was increased with tofacitinib, with an incidence rate of 2.91 (95% CI 2.27–3.74) (97) and higher risk of all infections, with an RR of 5.7 (95% CI 1.8–18.1) (48). Although this drug has an extremely short serum half-life, little is known about the duration of immunosuppression after the drug is withheld, although indirect translational data suggest that host defense returns to normal at 7 days. Therefore, the Panel recognized that the recommendation for the duration of withholding may change in the future, as physician and patient experience with this drug grows (41,47,48,51,77,79,97,98).

4. Severe SLE (as defined in Table 1)

Continue the current dose of methotrexate, mycophenolate mofetil, azathioprine, cyclosporine,

or tacrolimus through the surgical period in all patients undergoing THA or TKA (Table 2).

There is a great deal of uncertainty and little published experience regarding risks associated with perioperative medication management in patients with severe SLE. There is, however, indirect evidence concerning organ transplant patients who continue anti-rejection therapy through the surgical period (99,100). The caveat to this analogy is that the time course of organ rejection after withholding immunosuppressant medication may be different from the time to SLE flare after withholding medications. These considerations led to the recommendation to continue the current dose of methotrexate, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus through the surgical period in all patients with severe SLE. Nevertheless, the Panel felt that decisions regarding elective surgery in patients with severe SLE should be made on an individual basis with the patient's rheumatologist.

5. Not-severe SLE (as defined in Table 1)

Withhold the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus 1 week prior to surgery in all patients undergoing THA or TKA (Table 2).

For patients with not-severe SLE, the time course to flares after withholding medications is not known, while there is a known infection risk associated with these medications. The Panel felt that careful monitoring of the patient after surgery would permit restarting the medications prior to clinical flares in patients with not-severe SLE, for whom the morbidity of infection might outweigh the risk of a flare. These medications can be withheld 1 week prior to surgery, permitting some return of normal immune function, and restarted at 3–5 days after surgery in the absence of wound healing complications or infection at the surgical site or elsewhere. There are multiple mechanisms postulated for immunosuppression with these medications, including leukopenia, interference with T cell costimulatory signaling, and blocking the de novo pathway of purine synthesis, with different time courses for onset and reversal (101,102).

6. RA, SpA including AS and PsA, JIA, or SLE

Restart biologic therapy in patients for whom biologic therapy was withheld prior to undergoing THA or TKA once the wound shows evidence of healing (typically ~14 days), all sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no clinical evidence of non-surgical site infections (Table 2).

The decision to restart antirheumatic therapy can be based on evaluation of the patient's wound status and clinical judgment for absence of surgical and non-surgical site infections; wound closure is typically reached by 14 days. Therefore, biologic therapy can be restarted once the wound shows evidence of healing (typically ~14 days), all sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no clinical evidence of

Table 2. Recommendations for perioperative management of antirheumatic drug therapy in patients with rheumatic diseases undergoing elective THA or TKA *	
Recommendation/strength of recommendation (bold indicates conditional)	Level of evidence
<p>RA, SpA including AS and PsA, JIA, or SLE: Continue the current dose of methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine (nonbiologic DMARDs) for patients undergoing elective THA or TKA.</p> <ul style="list-style-type: none"> • RCTs of continuing vs. discontinuing DMARDs at the time of surgery revealed that the risk of infections was not increased, but in fact decreased, when DMARDs were continued, with an RR of 0.39 (95% CI 0.17–0.91) (37,38). Evidence indicates a low infection risk with these DMARDs in settings other than THA and TKA (39). • Disease flares after surgery occur frequently, and continuing DMARDs decreases the risk (RR 0.06 [95% CI 0.0–1.10]) (37,40), yet flares were significantly less important than infection for the Patient Panel. 	Low to moderate
<p>RA, SpA including AS and PsA, JIA, or SLE: Withhold all current biologic agents (see Figure 1) prior to surgery in patients undergoing elective THA or TKA, and plan the surgery at the end of the dosing cycle for that specific medication.</p> <ul style="list-style-type: none"> • RCTs (nonsurgical) demonstrated an increase in infection risk associated with use of all biologic agents (41–87). • Avoiding infection was significantly more important to patients than flares for patients with RA and JIA. • Meta-analysis and network meta-analysis revealed that infection risk for biologic agents is strongly associated with high-dose therapy and may not be associated with low-dose biologic agents (42). • Serum half-life may not correspond to the duration of the immune-suppressant effect, so the dosing cycle was chosen as more relevant in determining the withholding interval (88–91). • Until further studies have clarified and established differences in risk between biologic agents, there was insufficient evidence to support separating biologic agent management in the perioperative period (43–89). • For SLE, there was paucity of data supporting perioperative benefit in SLE (93–95). • A systematic review of rituximab vs. placebo (and occasionally vs. control treatment including nonbiologic DMARDs) in nonsurgical patients with RA and SLE revealed the risk of all serious adverse events with a range of RRs from 0.85 (95% CI 0.62–1.17) to 0.89 (95% CI 0.7–1.14) (59,92). • Observational studies reveal that patients with SLE, particularly those with active or severe SLE, are at a higher risk for adverse events after surgery. • Belimumab is indicated for use in not-severe SLE, which is not thought to increase perioperative risk (95,96). • As an example, using this guideline, patients treated with rituximab every 6 months would schedule their surgery, when possible, at the week after the first withheld dose during month 7. Patients receiving belimumab, which is given every 4 weeks, would schedule their surgery during week 5. • Patients treated with adalimumab, dosed at 2-week intervals, would plan their surgery in week 3, while patients treated with infliximab, when dosed every 8 weeks, would schedule their surgery in the week after the first withheld dose during week 9. 	Low
<p>RA, SpA including AS and PsA, or JIA: Withhold tofacitinib for at least 7 days prior to surgery in patients undergoing THA or TKA.</p> <ul style="list-style-type: none"> • Indirect evidence from systematic reviews and meta-analyses of tofacitinib vs. placebo (and occasionally vs. control treatment including nonbiologic DMARDs) in nonsurgical patients shows that the risk of serious infections was increased with tofacitinib with an incidence rate of 2.91 (95% CI 2.27–3.74) (97) and higher risk of all infections with an RR of 5.7 (95% CI 1.8–18.1) (48). • Although this drug has an extremely short serum half-life, little is known about the duration of immunosuppression after the drug is withheld. Therefore, the Panel recognized that the recommendation for the duration of withholding may change in the future, as physician and patient experience with this drug grows (41,47,48,51,77,79,97,98). 	Low
<p>Severe SLE: Continue the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus through the surgical period in all patients undergoing THA or TKA (see Figure 1).</p> <ul style="list-style-type: none"> • The Panel recognized that there is a great deal of uncertainty and little published experience regarding risks associated with perioperative medication management in patients with severe SLE. • Indirect evidence with organ transplant patients supports continuing anti-rejection therapy without interruption at the time of surgery (99,100). • Decisions regarding elective surgery in patients with severe SLE should be made on an individual basis with the patient's rheumatologist. 	Low

(continued)

Table 2. (Cont'd)

Recommendation/strength of recommendation (bold indicates conditional)	Level of evidence
<p>SLE (not severe): Withhold the current dose of mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus 1 week prior to surgery in all patients undergoing THA or TKA.</p> <ul style="list-style-type: none"> • The time course to flares in not-severe SLE is not known. • The morbidity of prosthetic joint infection may be more severe than a flare in SLE that is not severe. • These medications can be withheld 1 week prior to surgery, permitting return of some immune function, and restarted at 3–5 days after surgery in the absence of wound healing complications or infection at the surgical site or elsewhere. • There are multiple mechanisms postulated for immunosuppression with these medications, including leukopenia, interference with T cell costimulatory signaling, and blocking the de novo pathway of purine synthesis, with different time courses for onset and reversal (101,102). • Suggest a conservative withhold of 7 days prior to surgery until additional research increases understanding of these medications. 	Low
<p>RA, SpA including AS and PsA, JIA, or SLE: Restart biologic therapy in patients for whom biologic therapy was withheld prior to undergoing THA and TKA once the wound shows evidence of healing (typically ~14 days), all sutures/staples are out, there is no significant swelling, erythema, or drainage, and there is no clinical evidence of non-surgical site infections, rather than shorter or longer periods of withholding.</p> <ul style="list-style-type: none"> • The decision to restart antirheumatic therapy should be based on careful assessment of the patient's wound status and clinical judgment for absence of surgical and non-surgical site infections. Normal wound closure typically requires ~14 days. 	Low
<p>RA, SpA including AS and PsA, or SLE: Continue the current daily dose of glucocorticoids in patients who are receiving glucocorticoids for their rheumatic condition and undergoing THA or TKA, rather than administering perioperative supra-physiologic glucocorticoid doses (so-called “stress dosing”).</p> <ul style="list-style-type: none"> • This recommendation specifically refers to adults with RA, AS, PsA or SLE who are receiving glucocorticoids for their rheumatic condition, and does not refer to JIA patients receiving glucocorticoids who may have received glucocorticoids during childhood developmental stages, or to patients receiving glucocorticoids to treat primary adrenal insufficiency or primary hypothalamic disease. • The literature review found information on hemodynamic instability in a systematic literature review on patients with rheumatic diseases whose mean prednisone (or equivalent) dose was ≤ 16 mg/day. • The CDC considers the cut-off for immunosuppression at 20 mg of prednisone/day for at least 2 weeks, and observational studies demonstrate an increase in arthroplasty infection risk with long-term steroid use > 15 mg/day. • Optimization for THA and TKA should include carefully tapering the glucocorticoid dose prior to surgery to < 20 mg/day, when possible (102,103). 	Low
<p>* THA = total hip arthroplasty; TKA = total knee arthroplasty; RA = rheumatoid arthritis; SpA = spondyloarthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis; JIA = juvenile idiopathic arthritis; SLE = systemic lupus erythematosus; DMARDs = disease-modifying antirheumatic drugs; RCTs = randomized controlled trials; RR = relative risk; 95% CI = 95% confidence interval; CDC = Centers for Disease Control and Prevention.</p>	

non-surgical site infections. There is no direct evidence regarding the optimal time to restart medication after surgery, but standard precautions for biologic agents warn against use in patients with an active infection or in high-risk settings, such as with an open wound.

7. RA, SpA including AS and PsA, or SLE

Continue the current daily dose of glucocorticoids in adult patients with RA, SpA including AS and PsA, or SLE who are receiving glucocorticoids for their rheumatic condition and undergoing THA or TKA, rather than administering perioperative supra-physiologic glucocorticoid doses (so-called “stress dosing”) (Table 2).

Hemodynamic instability/hypotension and infection risk were 2 specific areas of concern with regard to perioperative glucocorticoid dosing. Regarding hemodynamic instability, the recommendation to continue the current daily dose of glucocorticoids in adult patients who are receiving glucocorticoids, rather than administering

perioperative supra-physiologic glucocorticoid doses (“stress dosing”), specifically refers to adults with RA, AS, PsA, or SLE who are receiving glucocorticoids (≤ 16 mg/day prednisone or equivalent) for their rheumatic condition; it does not refer to JIA patients receiving glucocorticoids who may have been treated with glucocorticoids during childhood developmental stages, or to patients receiving glucocorticoids to treat primary adrenal insufficiency or primary hypothalamic disease. Low-quality RCT evidence (rated down for indirectness due to varying glucocorticoid doses, heterogeneity of surgical procedures, and imprecision due to small numbers) and evidence from observational trials summarized in a systematic review suggested that there was no significant hemodynamic difference between those patients given their current daily glucocorticoid dose compared to those receiving “stress-dose steroids” (103).

Regarding the infection risk, the Panel noted that the cutoff for immunosuppression according to the Centers for Disease Control and Prevention was 20 mg/day of prednisone for at least 2 weeks, in the context of risk

associated with the administration of live vaccines. In addition, observational studies demonstrate an increase in infection risk following TJA for long-term users of glucocorticoids at doses of >15 mg/day. A patient in optimal condition for elective THA or TKA would be receiving a dose of prednisone or equivalent that was <20 mg/day, when possible, and receive their usual daily dose rather than the “stress dose” in light of the effect on infection risk (102,103).

DISCUSSION

The 2017 ACR/AAHKS guideline for the perioperative management of antirheumatic drug therapy for adults undergoing elective THA and TKA was designed for use by clinicians and patients during the perioperative period. Included recommendations address the use of treatment with antirheumatic drugs (including DMARDs, tofacitinib, biologic agents, and glucocorticoids) for the adult patient with RA, SpA including AS and PsA, JIA, or SLE, recognizing that antirheumatic medication is frequently used at the time of THA or TKA, and that rates of infection and adverse events, including readmission, are increased in this population. The optimal management of antirheumatic medications to treat these diseases may mitigate risks. We have used GRADE methodology to synthesize the best available evidence and have been transparent regarding both the strength of the recommendation and the limited quality of the evidence for each recommendation.

This project brought together major stakeholders (orthopedic arthroplasty surgeons, rheumatologists, methodologists, and patients) to create a patient-centric, expert-led group to determine optimal management of these high-risk patients through a group consensus process. To date, there has been little to no consensus among orthopedic surgeons or rheumatologists on the optimal way to manage antirheumatic medications during the TJA perioperative period, which often leads to uncertainty in decision-making for physicians and patients alike.

A major limitation of this guideline is the paucity of high-quality, direct evidence regarding medications and perioperative risk of infection and flare. The indirect nature of the evidence was the primary reason the quality of evidence was considered low, which led to a conditional designation for all the recommendations. Nonetheless, because patients with rheumatic diseases frequently undergo THA and TKA while receiving DMARDs and biologic agents, we sought to fulfill the need for guidance based on the best available evidence and agreement among stakeholders. The Patient Panel thought infection risk was much more important than flare risk, and this drove the direction of the recommendations (uniformly in favor of withholding any medications in which evidence from non-operative populations suggested an increase in infection).

Topics such as cardiac risk, deep venous thrombosis risk, risk of 90-day readmissions, and management and care of the cervical spine are related to the perioperative care of patients with rheumatic disease who are undergoing THA or TKA. The guideline was limited, however, to

risks attributable to perioperative management of antirheumatic drug therapy.

Antirheumatic medications and disease states were initially evaluated individually. Due to a lack of evidence, however, for each individual medication and disease state, the medications were combined by category and diseases, with the exception of SLE.

With regard to patients with SLE, the Panel recognized that recommendations for perioperative medication management in a complex disease such as SLE would be challenging, as SLE is frequently complicated by multiple organ involvement, as well as complex or unusual medication regimens. Moreover, SLE flares may be organ-threatening, and SLE patients may be more averse to risk of flare than to infection; therefore, the lack of SLE patients on the Patient Panel was a limitation. Nonetheless, the orthopedic and rheumatology stakeholders felt strongly that perioperative medication management guidance was needed for SLE patients.

The recommendation to restart biologic agents was based on the patient’s wound healing (generally requiring a minimum of 14 days) and clinical judgment for the absence of both surgical site and non-surgical site infection. While there are differences in practice patterns and many patients do not return to their surgeon within 2 weeks of discharge, screening mechanisms to assess the wound, including utilizing visiting nurse services, and taking photographs of the wound for review by e-mail, smartphone, or other mobile health technologies, would help to identify those who should be evaluated in person prior to restarting biologic agents.

The Voting Panel thought it worthwhile to suggest a research roadmap for future studies that could be conducted as part of a collaboration between the 2 organizations. The team discussed the following topics and recommended that they be targeted for future research: 1) Perioperative glucocorticoid management. While the RCT data support continuing the current glucocorticoid dose rather than “stress dosing,” limited numbers of patients and heterogeneity of dose, diagnosis, and surgical procedure leave us with only low-quality evidence; 2) Perioperative management of biologic agents. The Voting Panel suggested investigating existing biologic agents through registries and administrative databases, as well as planning multicenter RCTs to define the optimal medication management strategy; and 3) Perioperative management of DMARDs. Currently, data from RCTs for patients undergoing surgery reflect older, lower-dose regimens for methotrexate, and studies of leflunomide include small numbers of patients. Multicenter RCTs should be performed to determine the optimal perioperative management regimens and include assessment of comorbidities and glucocorticoid use in the study design.

The recommendations that form this guideline are not treatment mandates, but can be used to provide guidance and promote discussion regarding medication management prior to surgery. The authors recognize that not all potential perioperative clinical scenarios are covered by this guideline, but the most common clinical scenarios are addressed. This guideline does not replace perioperative clinical assessment and optimization, and does not

preclude a discussion of the risks and benefits of surgery as patients and their physicians prepare for THA and TKA.

In summary, this guideline provides clinicians and patients with a working document regarding how to manage antirheumatic drugs in the time leading up to elective THA and TKA. The recommendations provide important guidance that was informed by the available literature, clinical expertise and experience, and patient values and preferences. The acknowledgment of low-quality evidence in this area should lay the foundation for future research.

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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 published. Dr. S. 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.

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