

**ACR-AAHKS Guideline for the Perioperative
Management
of Anti-rheumatic Medications in Patients with
Rheumatic Diseases Undergoing Elective Total Hip or
Knee Arthroplasty**

Bryan D. Springer, MD

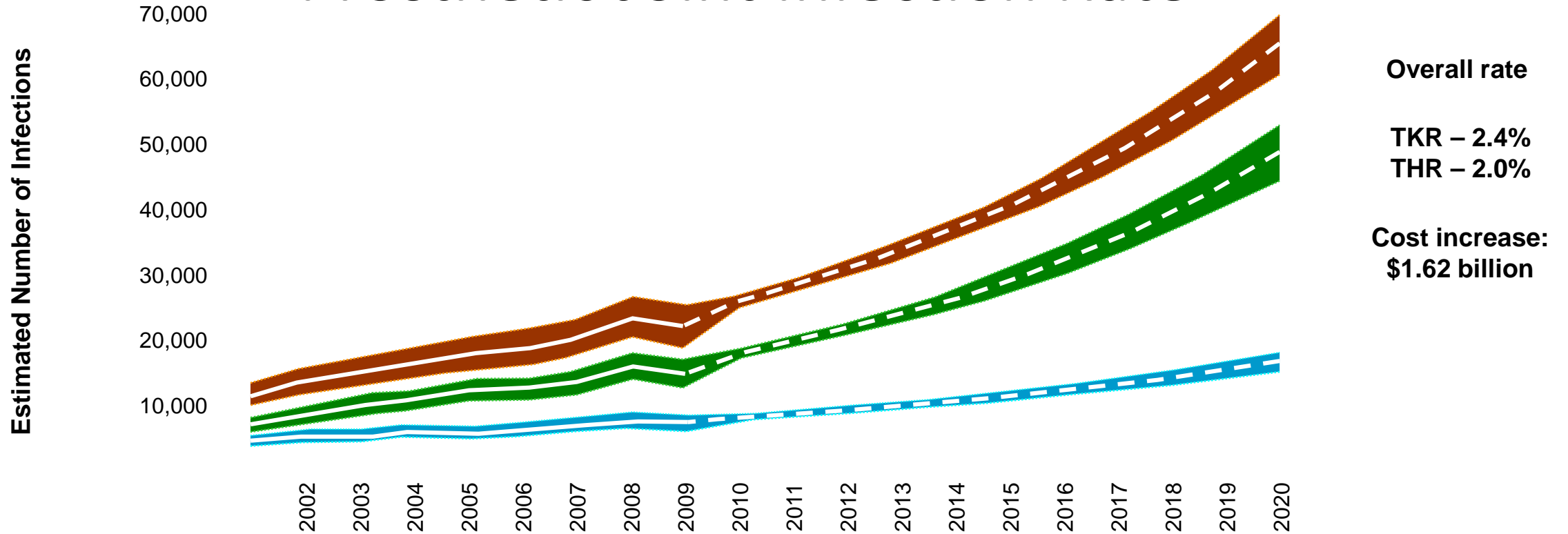
Thank You AAHKS Members

- 3 years in the making
- Weekly conference calls of Core Leadership Team
- Literature Review Team
- Expert Panel
- Voting Panel
- Patient Panel
- Chick Yates, MD
- Matt Abdel, MD
- Vin Dasa, MD
- Jeremy Gilliland, MD
- Antonio Chen, MD
- Alex Sah, MD
- Louis Stryker, MD
- Mark Goodman, MD
- Scott Sporer, MD
- Michael Mont, MD
- Peter Sculco, MD

Rates of Arthroplasty Remain High among Rheumatic Disease Patients

- The widespread use of DMARDs and biologics has not decreased the utilization of arthroplasty
- 34-58% of RA patients undergo orthopedic surgery including arthroplasty over 30 years^{1,2}
- Rates of arthroplasty are increasing for SLE and Spondyloarthritis (Psoriatic, Ankylosing Spondylitis) patients ⁵

Prosthetic Joint Infection Rate

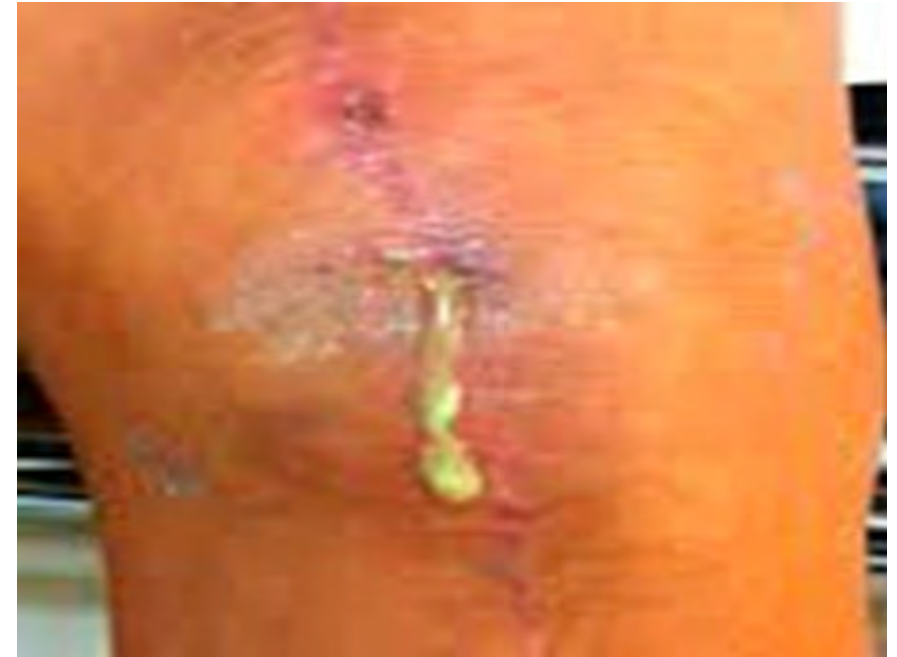


Historical and projected number of infected THA, TKA, and total (THA + TKA) procedures in the United States (2001-2020). The dashed lines represent the projected values per surgery type

RA and SLE Patients have an Increased Risk of Perioperative Infections

- **RA** pooled meta-analysis
 - **HR 1.47 -1.83** for PJI
- 90 day readmission increasing- most commonly for infection
- 2009: OR 0.89 (95% CI 0.46-1.87)
- 2010: OR 1.34 (95% CI, 0.69-2.61)
- 2011: OR1.74 (95% CI, 1.16-2.60)

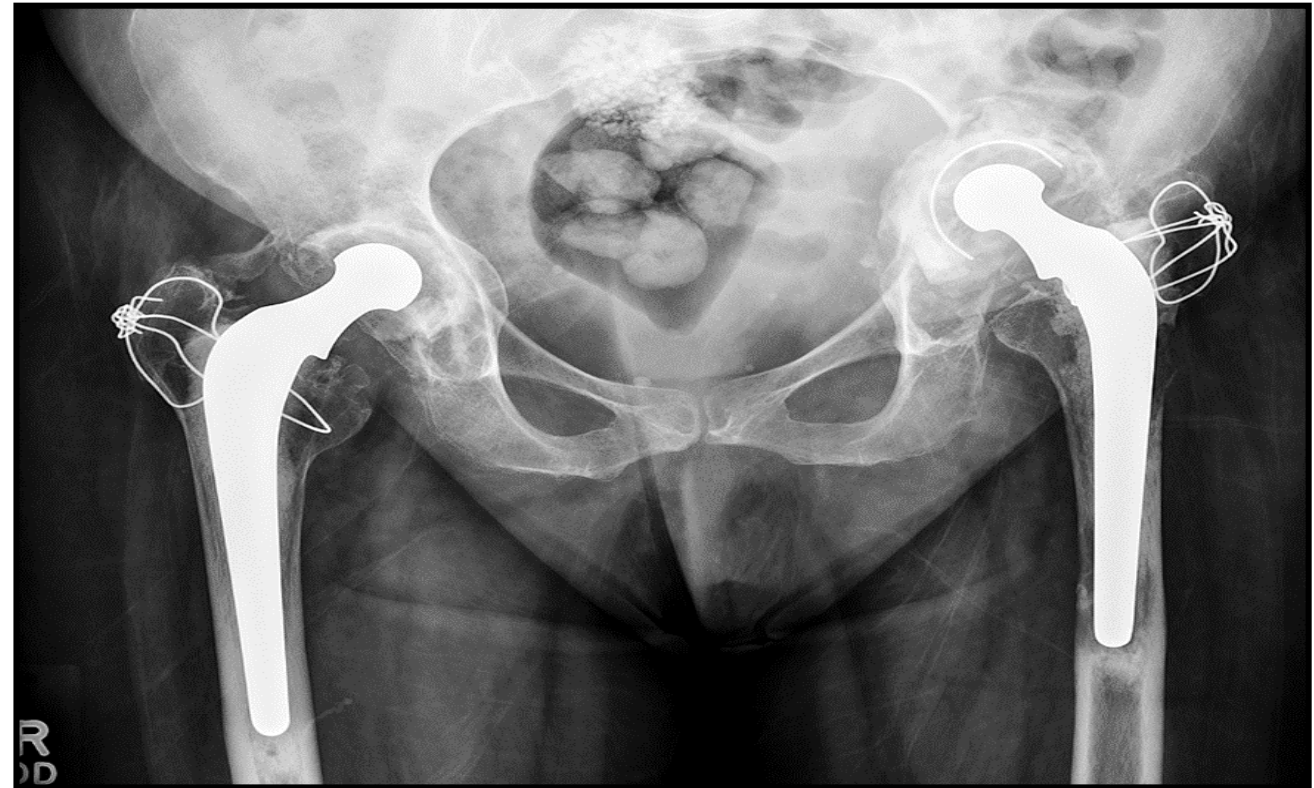
- **SLE-Sepsis** OR 3.43 (95% CI 2.48- 4.74)



Increased medical and surgical complexity

Disease specific risks

- Co-morbidity burden
- Age, gender
- Disease Activity
- Disease Severity
- Overall disability
- Presence of a prosthetic joint
- **Medications: most accessible modifiable infection risk factor**



SLE Severity/Activity Predicts Post-Op Clinical Outcomes

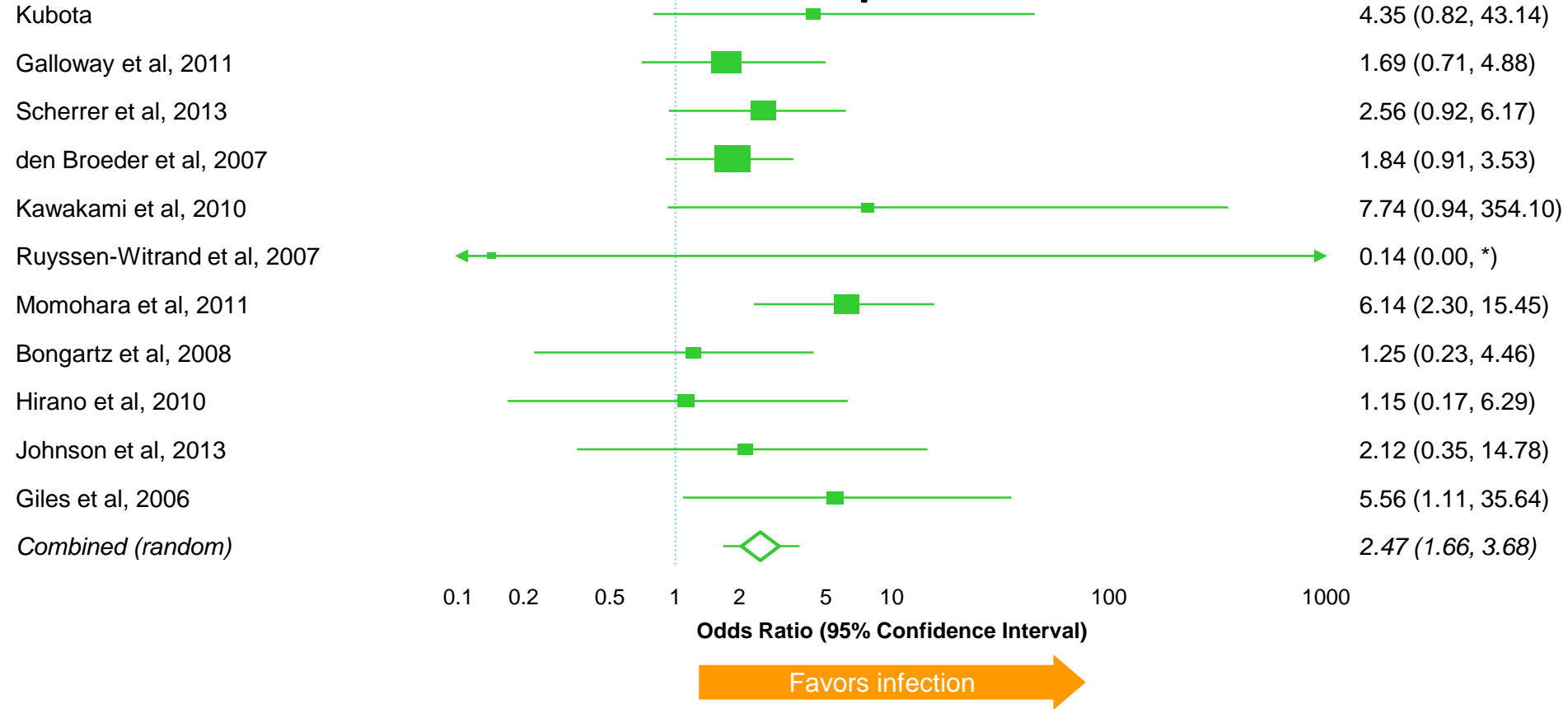
| Outcome | Outpatient SLE N=2746 | | Hospitalization within 24 months N=1575 | | Hospitalization within 6 months N=1214 | |
|------------------|-----------------------|-----------|---|------------------|--|------------------|
| | OR | 95% CI | OR | 95%CI | OR | 95%CI |
| MI | 0.97 | 0.41-2.28 | 1.42 | 0.52-3.88 | 1.56 | 0.51-4.76 |
| Renal failure | 1.54 | 0.93-2.56 | 5.87 | 3.76-9.17 | 7.23 | 4.52-11.6 |
| PE | 2.29 | 0.63-8.32 | 3.63 | 0.91-14.5 | 4.86 | 1.20-19.7 |
| Sepsis | 1.14 | 0.83-1.56 | 2.99 | 2.21-4.04 | 3.43 | 2.48-4.74 |
| Stroke | 0.71 | 0.51-1.0 | 1.59 | 1.11-2.27 | 2.01 | 1.38-2.92 |
| Any above | 0.98 | 0.82-1.15 | 1.94 | 1.62-2.32 | 2.30 | 1.89-2.80 |
| 30 day mortality | 1.36 | 0.77-2.43 | 2.26 | 1.26-4.04 | 2.39 | 1.28-4.45 |

analysis using Taiwan's national insurance research database, age and sex matched controls and Stratified by

High Perioperative Exposure to Immunosuppressants

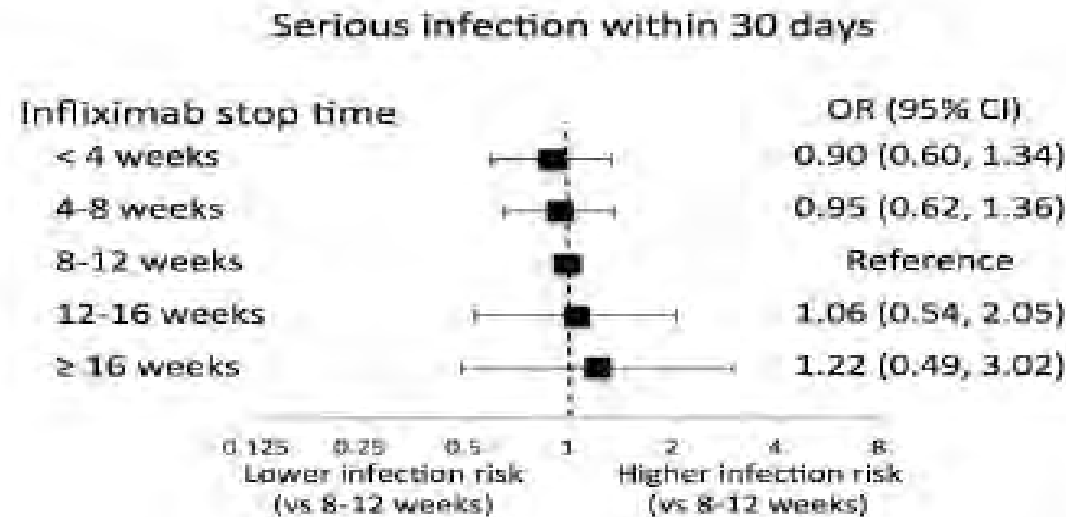
- 75% -84% of RA undergoing THR or TKR take DMARDs or biologics¹
- 80% of RA patients undergoing orthopedic surgery take glucocorticoids
- 75% pf patients with SLE are on immunosuppressant medications at the time of surgery

TNFi Treated Arthroplasty Group More Likely to Develop SSI

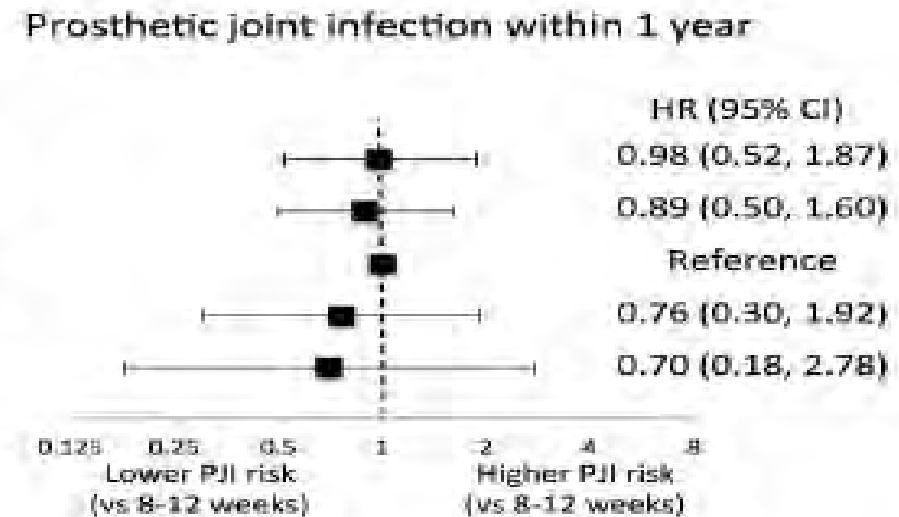


Odds ratio meta-analysis plot (random effects)

Infliximab within 4 weeks of THA or TKA was not associated with a higher risk of serious infection



Propensity adjusted odds ratio



Propensity adjusted hazard ratio

Inconsistent Perioperative Use

| Anti-TNF | Stop Time weeks \pm SD n=71 | Restart Times weeks \pm SD n=23 |
|---|---|---|
| Etanercept (n=59) Standard dosing: weekly | 2.4 \pm 2.4 (n=39) range 1-14 | 2.1 \pm 1.1 (n=15) range 1-14 |
| Golimumab (n=2) Standard dosing: monthly | 8 (n=1) range NA | 1.5 (n=1) range NA |
| Adalimumab (n=25) Standard dosing: every 2 weeks | 5 \pm 5.6 (n=20) range 1-24 | 2 \pm 1 (n=3) range 1-3 |
| Infliximab (n=18) Standard dosing: every 4-8 weeks | 4.8 \pm 2.2 (n=11) range 2-9 | 4.4 \pm 1.8 (n=4) range 2-4 |

Management of Anti-rheumatic Medication may Mitigate Risk

- Periprosthetic joint infection (PJI) remains one of the most common modes of failure following arthroplasty
 - Associated with increased morbidity, significant healthcare expenditure, poor function outcomes, and mortality
- Most infection risk factors are not modifiable- age, disease severity, overall disability

How to Manage These Medications ?

- No current guidelines to direct physicians and patients on management of these medications in the perioperative period
- Guidance is needed for common clinical situations even where data is sparse
- This project brought together major stakeholders – arthroplasty surgeons, rheumatologists, methodologists and patients



Guideline Development Process

Define team/project scope, identify important questions and outcomes

Obtain feedback via public comment on project plan document

Define

Search for relevant evidence

Evaluate strengths and weaknesses of individual studies

Evaluate strength of body of evidence for outcomes

Weigh benefits and harms

Decide direction and strength of recommendation

Draft guideline

ACR/AAHKS + journal peer review and approval

Publish/disseminate guideline

Periodic lit search updates, annual reevaluation re: need for updating/revision



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PUBLISH

Guideline Scope

- Adults with RA, SpA, including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), adults with juvenile idiopathic arthritis (JIA), or SLE who are undergoing elective THA or TKA
 - Should anti-rheumatic medications be withheld prior?
 - If withheld, when should they be stopped?
 - If withheld, when should they be restarted after surgery?
 - In patients using GCs, what dose should be administered at time of surgery?

All Recommendations in this Guideline are Conditional due to the Quality of the Evidence

- There were no RCTs for periop use of biologics
- Observational studies are typically rated as low
- Conditional recommendations are **preference sensitive** and warrant shared decision-making
 - Require estimating the relative value patients place in the outcomes
 - Apply to the majority, but not all
 - Additional research might change the recommendation

Patient Panel: *Estimating the Relative Value of the Outcomes*

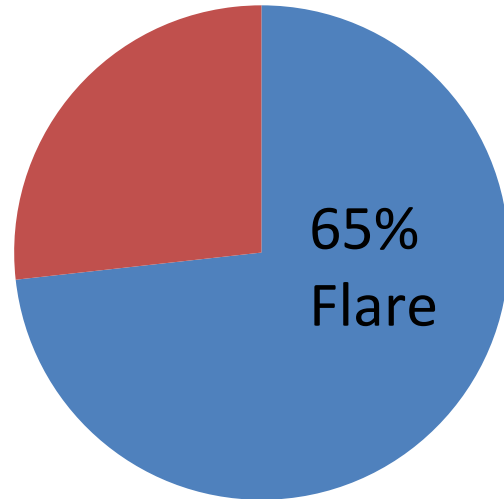
- Patient panel – 11 adults with RA and JA
 - All had THA or TKA (1-8)
 - 1 reported prosthetic joint infection

Patients carefully reviewed data, recognized that flares were quite common and infection was rare

Patients were MUCH more willing to risk flare than infection

Patient panel -100% concordant with the expert panel

Flares vs. Infection Risk?



- 65% of RA patients flare after THA and TKA
- Effect on long term arthroplasty outcome unknown



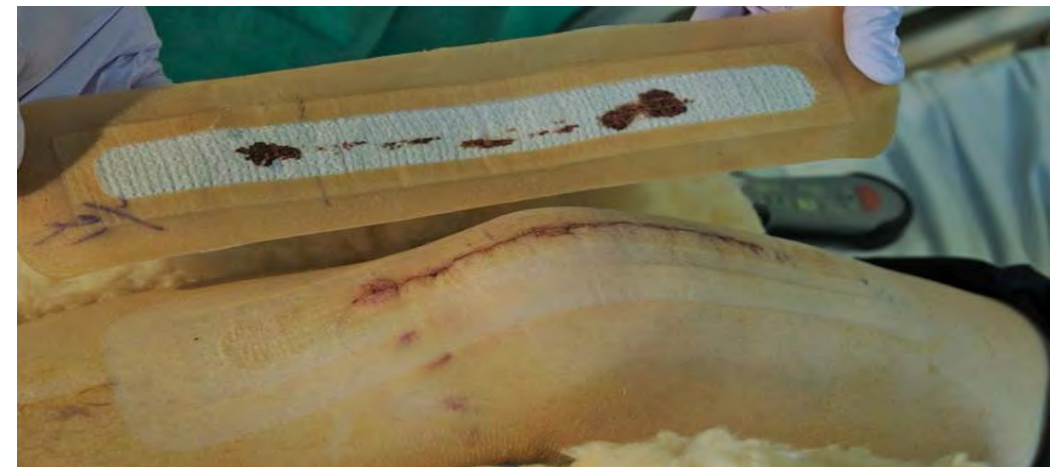
Pharmacokinetics vs Pharmacodynamics

| DRUG | Serum half life | Standard dose interval |
|-------------|---|---|
| Adalimumab | 2 weeks | Every other week |
| Etanercept | 102 hours (single 25mg dose) | Weekly or twice weekly |
| Golimumab | 2 weeks | Monthly (SQ) Every 8 weeks (IV) |
| Infliximab | 7.7-9.5 days | Every 4 -8 weeks |
| Abatacept | 13.1 days (IV) 14.3 days (SQ) | Monthly (IV) Weekly (SQ) |
| Tocilizumab | Up to 11 days (4mg/kg IV) Up to 13 days (8mg/kg IV, 162 mg weekly) 5 days (162 mg eow SQ) | Every 4 weeks (IV) Every other week or weekly (SQ) |
| Secukinumab | 22-31 days | Every 4 weeks |
| Ustekinumab | 14.9-45.6 days | Every 12 weeks |
| Rituximab | 18 days | Two doses every 4-6 months |

1. RA, SpA, JIA or SLE: Continue methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine

- RCTs of continuing vs. discontinuing DMARDs revealed decreased risk of infections when DMARDs were continued, (RR of 0.39 (95% CI 0.17-0.91))
- Infection risk low DMARDs in settings other than THA and TKA
- Continuing DMARDs decreases the risk of flare [RR 0.06 (95% CI 0.0-1.10)]

- 54 yo woman with severe RA with R knee pain and deformity, on weekly methotrexate, adalimumab every 2 weeks, and prednisone 7.5 mg daily.
- She was indicated for TKR, which was performed 2 1/2 weeks after the last dose of adalimumab, she continued MTX, and received prednisone 7.5 mg on the morning of surgery.
- Surgery was uneventful, she resumed adalimumab on post-op day 14, after sending a photo of the wound to her surgeon



Withhold all biologics prior to surgery

Plan the surgery at the end of the dosing cycle for that specific medication

EXAMPLE: SLE patients treated with rituximab every 6 months would schedule their surgery when possible in 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

EXAMPLE: Patients treated with adalimumab, routinely dosed at 2-week intervals, would plan their surgery during 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

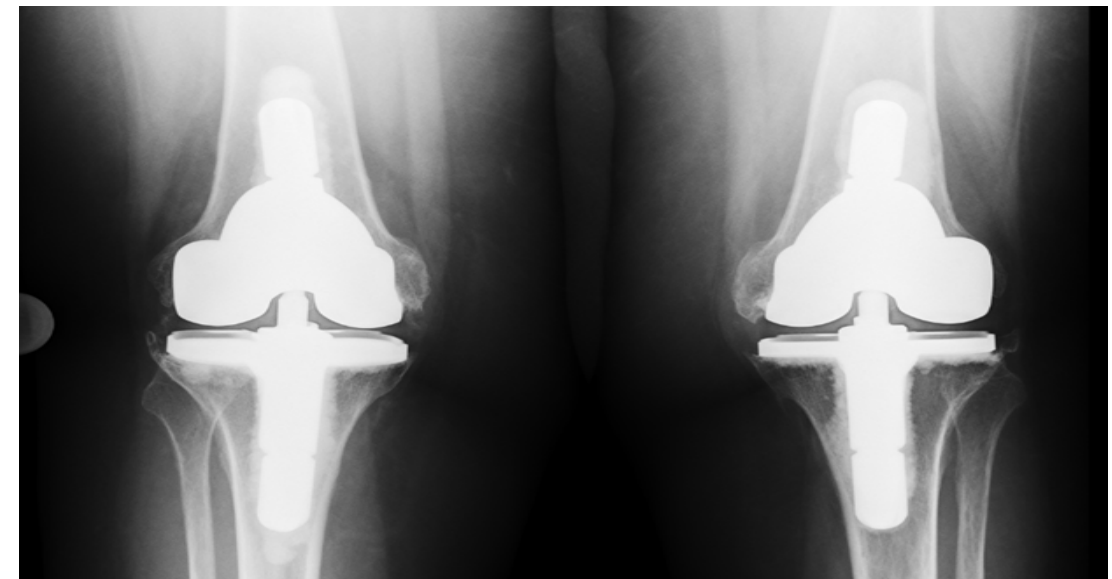
Rationale: Withhold Biologics

- Not answered in the literature
- The evidence from non-surgical RCTs demonstrated an increase in infection risk associated with use of all biologics
 - Most odds/hazards/risk ratios ~ 1.5 (range, 0.61 to 8.87)
- SLR did not support a differential risk for serious infection among biologics

Rationale: Withhold Biologics

- Infection risk for biologics is strongly associated with high-dose therapy (higher than standard) and may not be associated with low-dose biologics
- Serum half-life may not correspond to the duration of the immune-suppressant effect, so the dosing cycle was chosen as more relevant

- 44 yo woman with sero-positive RA presented in a wheelchair on leflunomide and golimumab.
- Exam revealed flexion deformities of both knees. She was indicated for BTKR.
- Leflunomide was continued and the surgery was planned 5 weeks after her golimumab dose.
- Her course was complicated by a PE, but she ultimately did well and by week 3 was ambulating with a walker. Her meds were re-started post-op week 2.



Rationale: Withhold Biologics in SLE

- Not answered in the literature
- Observational studies -patients with active or severe SLE are at a higher risk for post-op adverse events
- Rituximab is not FDA approved for use in SLE
- Belimumab is not approved for manifestations of severe SLE
- Data did not support separating the biologics

3. RA, SpA, or JIA: Withhold tofacitinib at least 7 days prior to surgery

- SLR and meta-analysis show an increased risk of serious infections
 - Incidence rate (IR) 2.91 (95% CI 2.27-3.74)
- Little is known about the duration of immunosuppression
- Indirect translational data suggests that host defense returns to normal at 7 days

Strand V. Arthritis Res Ther. 2015;17:362; 99. Boyle DL. Et al. Ann Rheum Dis. 2015;74(6):1311-6.
Cohen S. Arthritis Rheumatol. 2014;66(11):2924-37.

4. Severe SLE: Continue mycophenolic acid, azathioprine, cyclosporine, or tacrolimus

- Indirect evidence with organ transplant patients who continue anti-rejection therapy
- **Caveat** – time course of organ rejection after withholding immunosuppressant medication may be different from the time to SLE flare
- Decisions regarding elective surgery in patients with severe SLE should be made on an individual basis with the patient's rheumatologist

5. SLE (not-severe): Withhold the current dose of mycophenolic acid, azathioprine, mizoribine, cyclosporine, or tacrolimus
 - Withhold 7 days prior to surgery through 3-5 days after surgery, in absence of wound healing complications or any infection

6. Restart biologic therapy once the wound shows evidence of healing (\approx 14 days), sutures/staples are out, no significant swelling, erythema or drainage, no clinical evidence of non-surgical site infections

- The decision to restart therapy should be based on evaluation of the patient's wound status and clinical judgment for absence of surgical and non-surgical site infections

7. Continue the current daily dose of glucocorticoids in adult patients with RA, SpA, or SLE, who are receiving glucocorticoids for their rheumatic condition, rather than administering perioperative supra-physiologic glucocorticoid doses

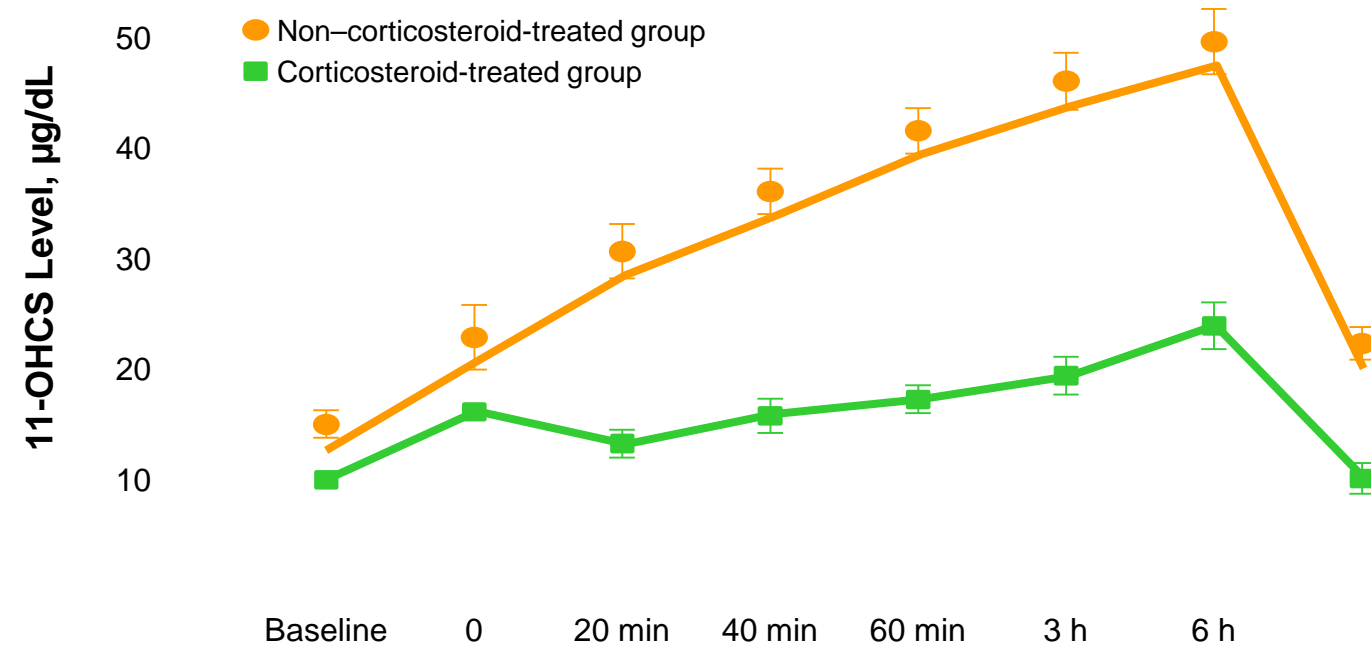
Rationale: Glucocorticoids

- SLR of RCT and observational studies demonstrated no significant hemodynamic difference, between patients given their daily glucocorticoid dose compared to those receiving “stress-dose steroids”
- Observational studies demonstrate an increase in infection risk following TJA for users of chronic glucocorticoids above 15 mg/day.
- Optimizing the patient for elective THA and TKA should include minimizing the daily glucocorticoid dose prior to surgery

No Hemodynamic Difference with Stress Dose Steroids

2 RCTs

- Chronic steroid treatment: CS stopped pre-op
- Lower steroid levels
- Stable hemodynamics



Plasma 11-hydroxycorticosteroid (11-OHCS) response to surgery in non-corticosteroid- and corticosteroid-treated patients with rheumatoid arthritis. Data from Jasani et al.

Rationale: Glucocorticoids

- The recommendation specifically refers to adults who are receiving glucocorticoids for their rheumatic condition
- Does not refer to patients with JIA who may have received glucocorticoids during development
- Does not refer to patients receiving glucocorticoids for primary adrenal insufficiency or primary hypothalamic disease.

Guideline Strengths

- This project brought together major stakeholders – orthopaedists, 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, and established a framework for further research
- Clear preference of the patient panel guided the strength and direction of the recommendations

Limitations

- Paucity of high-quality, direct evidence re: medications and perioperative risk
- Used indirect evidence from RCTs performed on patients who were not undergoing surgery to determine infection risk associated with included drugs and applied the data to these recommendations

Summary: Anti-rheumatic Medications and Arthroplasty

- Rate of arthroplasty remains high for patients with rheumatic diseases
- Use of DMARDs and biologics high at the time of surgery
- Complications are increased
 - increased infection risk consistently observed and significant when data are pooled
- Insufficient evidence to separate biologics
- Additional factors such as disease activity and severity, as well as smoking, corticosteroid use and diabetes may influence this increased risk

Unique perioperative challenges

- Optimal perioperative management requires close collaboration between orthopedists and rheumatologists
- Infection: medications appear to contribute to the risk of infection
 - Traditional DMARDs- MTX, HCQ, LEF appear safe in the perioperative period
 - Biologics should be withheld prior to surgery
 - SLE may need different management strategy

NEED FOR RESEARCH

- There is little direct evidence for medication related adverse events after THA or TKA
- Low incidence of surgical site infection increases practical challenges
- Will need multicenter studies to address these questions



Joint Publication of Guidelines

