

# PERIOPERATIVE MANAGEMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Dre Chantal Vallée, MD FRCPC  
Professeure agrégée, médecine interne



# CONFLICT DISCLOSURE

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- Definition: A conflict of interest may occur in situations when personal or professional interests of individuals may have actual, potential or apparent influence over their judgement and actions.
- No relevant conflict of interest or financial disclosure in regard with this presentation
- Speaker fees received in the past three years from Sanofi, Novo Nordisk, Bayer, Merck, AstraZeneca and Boehringer Ingelheim
- Dre Chantal Vallée, October 26<sup>th</sup> 2016



# OBJECTIVES

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- Perform a preoperative assessment of patients with rheumatoid arthritis (RA) and obtain appropriate preoperative tests in this population
- Manage immunosuppressive therapy in patients with RA and who are undergoing surgery (e.g. anti-TNF, methotrexate)
- Discuss the role of preoperative steroid stress dose in chronic steroid users



# TO BEGIN WITH...

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- 2-3 millions of surgery/year in Canada
- Increased complexity of patients
- Latest knowledge of and recommendations regarding treatment of specific disease states
- Preparing and optimizing patients
- Communication between clinicians



# OBJECTIVES FOR THE PREOPERATIVE ASSESSMENT

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- Identify which patients could be at increased risk for surgery
- Implement strategies to reduce the risk of surgery
- Review (optimize) general state of health



# PREOPERATIVE ASSESSMENT

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- History
- Physical examination
- Work-out according to risk
  - patient risk
  - surgery risk



# WHAT TO ASSESS

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- Cardiac conditions and risk factors
- Pulmonary diseases and risk factors
- Endocrine conditions
- Hematologic conditions
  - bleeding problems
  - thrombosis conditions and risk factors
- Medications
- Others





# QUESTION #1

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- Which of the following represent the major risk for surgery in rheumatoid patients?
  - 1. Infection
  - 2. Cardiovascular complications
  - 3. Rheumatoid flare
  - 4. Pain





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# PATIENTS WITH RHEUMATOID DISEASES

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- 60% of rheumatoid patients will need surgery
- Increased cardiovascular risk
- Immunosuppression and surgical site infections
- Steroid coverage
- States of altered coagulation
- Prediction of poor pain and function outcomes
  - Disease flare
    - pain and swelling
    - fatigue and inability to participate in activities



# CLINICAL SCENARIO

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- Mrs L.P., 72 years old to be evaluated for an elective hemicolectomy for diverticular bleeding
- Rheumatoid arthritis since age 54
  - leflunomide 200 mg every other day
  - prednisone 10 mg every day
  - infliximab 200 mg every 5 weeks
  - calcium, vitamin D, omeprazole and alendronate
- Type 2 diabetes on metformin, 500 mg twice a day, sitagliptine 100 mg every day, NPH 12 units at bedtime



# CLINICAL SCENARIO

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- No chest pain, no shortness of breath
- Can climb slowly one flight of 10 stairs
- Limited mostly by pain in her knees, but doesn't feel she would be able to do more without being short of breath
- BP 137-85, Pulse 92, weight 62 kg, exam otherwise normal
- EKG is normal, A1c 7.5%, creatinine 110



## QUESTION #2

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- ▶ What would be your next step?
- ▶ 1. Order a treadmill test
- ▶ 2. Order a nuclear stress test
- ▶ 3. Start bisoprolol at low dose before surgery
- ▶ 4. Send her for surgery without no more intervention





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# PREOPERATIVE CARDIAC ASSESSMENT

- Higher risk of cardiovascular disease
  - RA - SLE
  - 60% increase in CV death
  - mortality ratio 1.61 (95% CI 1.48 -1.75,  $P < 0.0001$ )
    - Meune, et al, Rheumatology (Oxford), 2009;48:1309-1313
  - more atypical symptoms of angina
    - Maradit-Kremers, et al, Arthritis Rheumatism, 2005;52:402-411





# PREOPERATIVE CARDIAC ASSESSMENT

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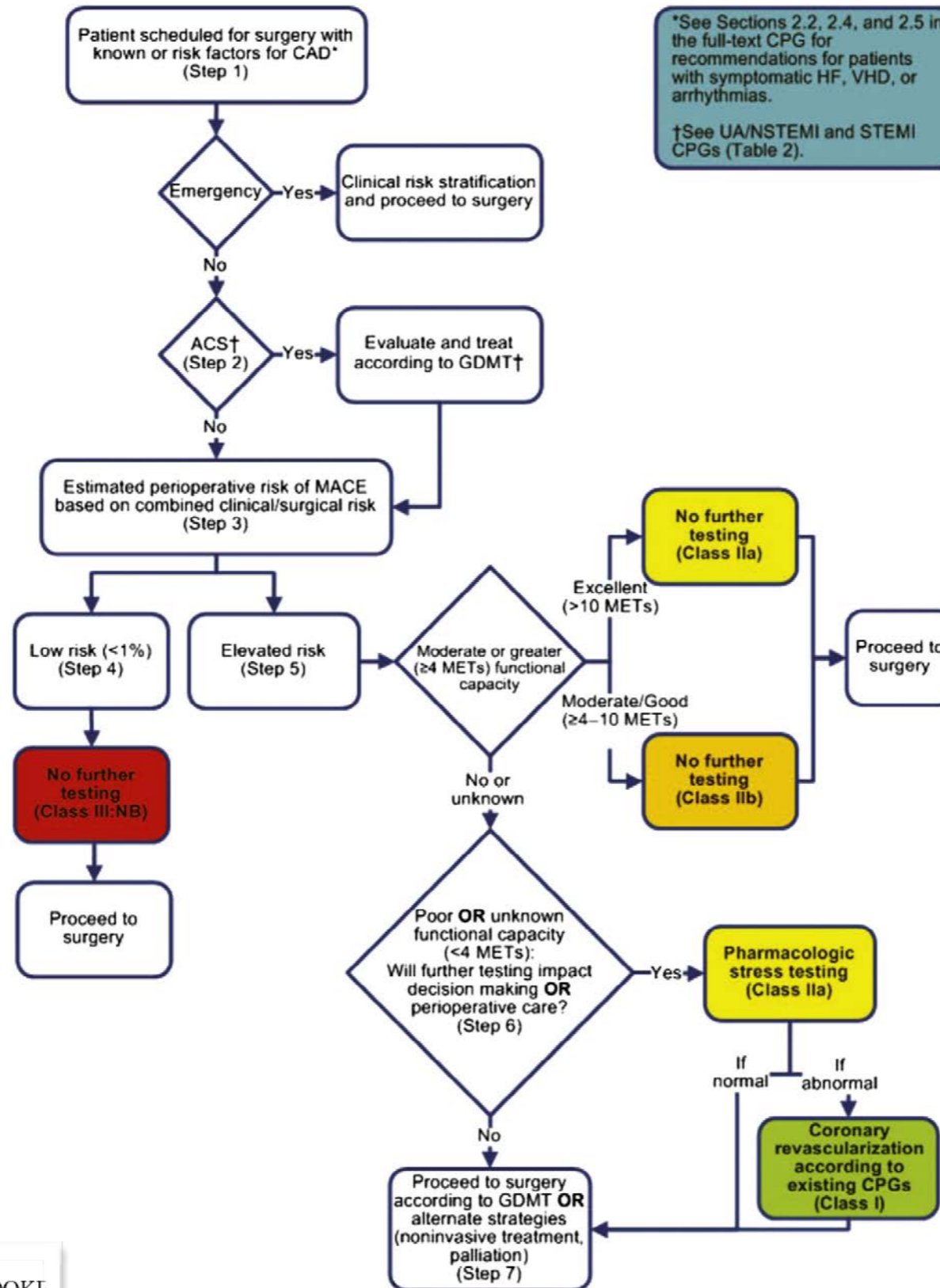
## ➤ Principles

- Intervention is rarely necessary to simply lower the risk of surgery
- No test such be performed unless likely to influence management



From: **2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**

J Am Coll Cardiol. 2014;64(22):e77-e137. doi:10.1016/j.jacc.2014.07.944



# CV RISK ASSESSMENT

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- 1. Is the surgery an emergency?
  - Yes?
    - Proceed
- 2. Is there active cardiac condition?
  - Yes?
    - Treat and stabilize
- 3. What is the risk of the surgery?
  - Low risk?
    - Proceed



# CV RISK ASSESSMENT

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- ▶ Does the patient have a good functional capacity?
  - ▶ Yes?
    - ▶ Proceed
  - ▶ Challenging here with rheumatoid conditions...
    - ▶ Limited activity - marker for increased CV risk
      - ▶ Gerson, et al, Annals of Internal Medicine, 1985;103:832-837



# CV RISK ASSESSMENT

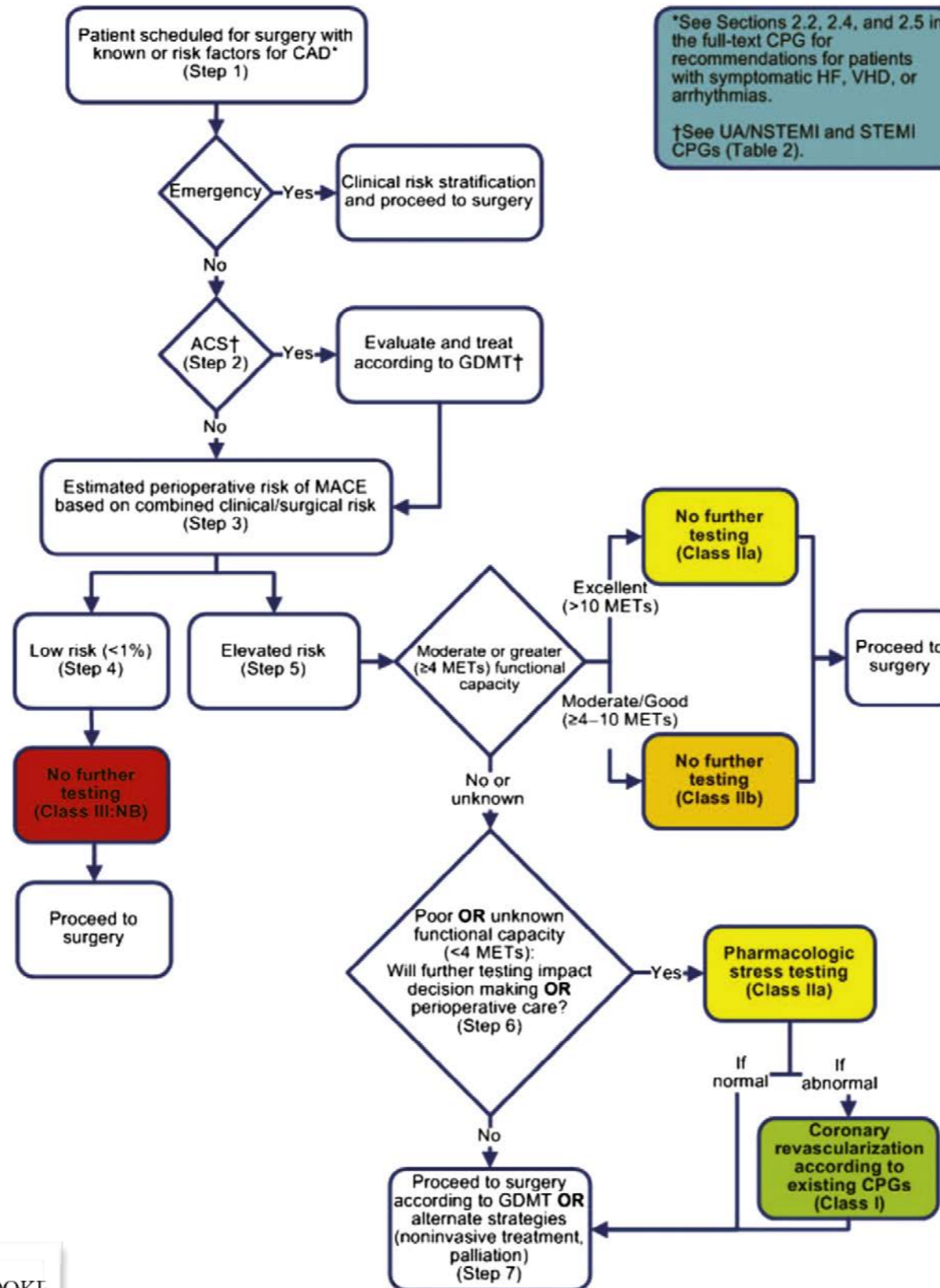
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- Presence of CV risk factors?
  - ischemic heart disease
  - heart failure
  - cerebrovascular disease
  - diabetes treated with insulin
  - renal insufficiency
  
- diagnosis of RA, psoriatic arthritis, ankylosing spondylitis or SLE???



From: **2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines**

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# CLINICAL SCENARIO, PART II

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- ▶ Nuclear stress test shows lateral ischemia, low intensity
- ▶ Bisoprolol 2.5 mg prescribed
  
- ▶ Patient heard about infectious risk
- ▶ Worried ++



# QUESTION #3

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- ▶ Which of the following is responsible for the worst surgical site infection risk?
  - ▶ 1. Infliximab
  - ▶ 2. Leflunomide
  - ▶ 3. Prednisone
  - ▶ 4. Rheumatoid arthritis







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# IMMUNOSUPPRESSION AND INFECTIOUS RISK

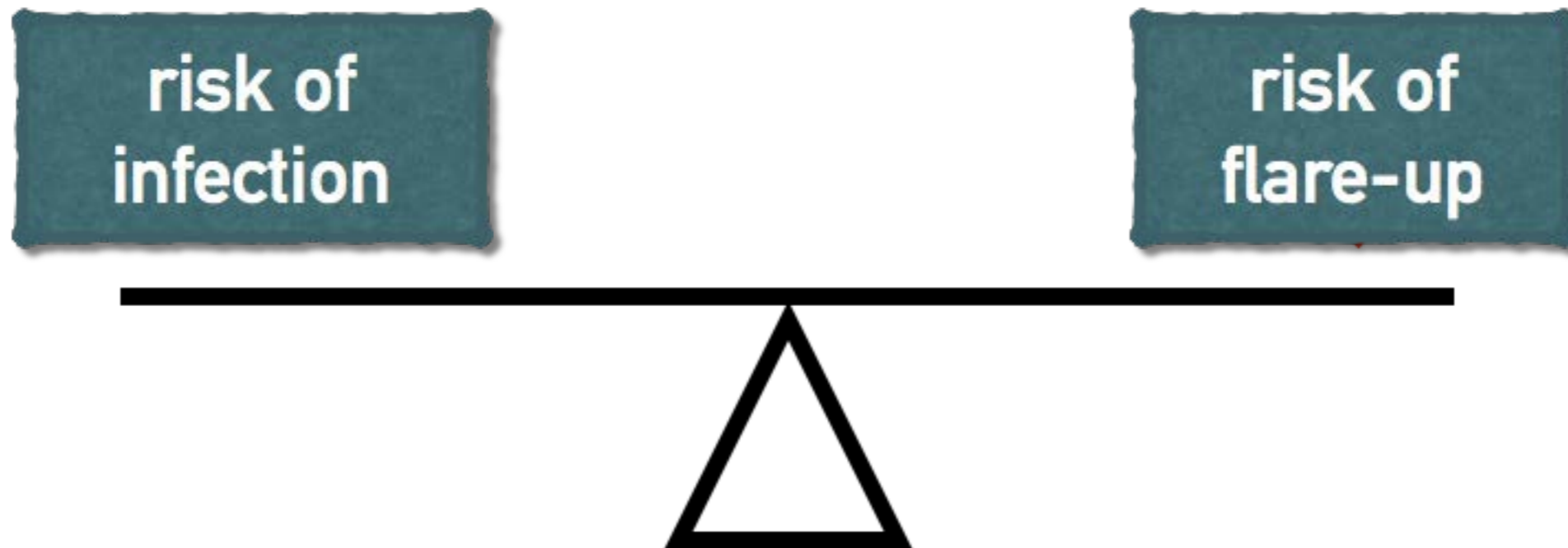
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- Controversy
- Sparse data
- Careful risk:benefit analysis
  - type and site of surgery
  - comorbidities
  - previous infections
  - type and dose of immunosuppression
  - risk of disease flare



# IN BETWEEN TWO RISKS

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# METHOTREXATE

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- One of the most commonly used
- More than 10 studies
  - largest presented by Grennan et al, 2001
  - no increase risk of infection or wound healing
  - more flare-ups in those who stopped 2 weeks before surgery



# METHOTREXATE

Study	Design	Patients (on MTX)	Recommendation
Murata et al (2006)	retrospective	124 (80)	continue
Bibbo et al (2003)	retrospective	104(104)	continue
Jain et al (2002)	retrospective	80(46)	continue
Grennan et al (2001)	prospective	388(88)	continue
Carpenter et al (1996)	prospective	32(13)	withhold
Escalante et al (1995)	retro/prostpective	204(?)	continue
Kasdan et al (1993)	retrospective	42(15)	continue
Sany et al (1993)	prospective	64(32)	continue
Perhala et al (1991)	retrospective	121(80)	continue
al (1991)	retrospective	38(19)	withhold



# METHOTREXATE

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- Recommendation:
  - SAFE to continue
    - Canadian Rheumatology Association, 2012 (Level I, Strength A)
  - Caution if comorbidities (renal, respiratory or hepatic)
    - could be withheld the week of and the week after the surgery



# LEFLUNOMIDE

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- ▶ Limited data
- ▶ Higher rate of postoperative wound-healing
- ▶ 1 prospective trial, 82 patients
  - ▶ same rate of infection in both group (1 continue, 1 stopped 2 weeks before up to 2 weeks after)
    - ▶ Tanaka et al, Journal of Clinical Rheumatology, 2003;9(2):115-118
- ▶ Long half-life (14 days)
- ▶ Recommendation
  - ▶ NOT to stop



# SULFASALAZINE

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- ▶ Limited data
- ▶ Half-life 6-10 hours
- ▶ Renal elimination
  
- ▶ Recommendation
  - ▶ To be withheld the day of the surgery if risk of AKI





# AZATHIOPRINE

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- ▶ Data in RA and in Crohn's disease
- ▶ Not associated with postoperative complication
- ▶ Half-life 5 hours
  
- ▶ Recommendation
  - ▶ SAFE to continue



# HYDROXYCHLOROQUINE

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- Did you know?
  - Have been used in the past to prevent postoperative venous thromboembolism
- Long half-life (40-50 days)
- Recommendation
  - SAFE to continue



# BIOLOGICS

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- ▶ Becoming a concern in preoperative assessment
  - ▶ growing number of biologics
  - ▶ growing number of indications
  - ▶ growing number of patients facing surgery
  - ▶ but very limited data
  
- ▶ In general, long half-life
  - ▶ days... sometimes months...
  
- ▶ If urgent surgery, proceed



# BIOLOGICS

Study	Design	Treatment groups	Outcome studied	Recommendation
Kawakami et al, 2010	retrospective case-control	Anti-TNF vs DMARDs	surgical site infection, DVT, disease flares	Anti-TNF more likely to cause SSI and DVT
Hirano et al, 2010	retrospective cohort	Anti-TNF vs DMARDs	wound healing, febrile episode, infections	No specific adverse effects
*den Broeder et al, 2007	retrospective parallel cohort	No anti-TNF vs Anti-TNF withheld vs continue	infection rates, wound healing	Anti-TNF not important risk factor
Ruysse-Witrand et al, 2007	retrospective	Discontinuation of anti-TNF at various time before surgery	complication rates	No difference
Giles et al, 2006	retrospective	Anti-TNF vs no anti-TNF	serious postop infections	Significant association with anti-TNF and post-op infections
Talwalkar et al, 2005	retrospective	Continuous anti-TNF vs stopped before surgery	infectious complications	No difference
Wendling et al, 2005	retrospective	Continuous anti-TNF vs stopped before surgery	infections, diseases flares	No difference
Bibbo & Goldberg, 2004	prospective	Anti-TNF vs DMARDs	infections, wound healing	No difference



# BIOLOGICS

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- ▶ Most data on anti-TNF agents
  - ▶ retrospective
  - ▶ varying definitions of exposure and outcomes
  - ▶ mostly orthopedic surgeries
  - ▶ underestimate risk of disease flares
    - ▶ problems with early mobilization
- ▶ in Crohn's disease, infliximab within 3 months of surgery associated with increase risk of postop sepsis, abcess and readmission
  - ▶ Appau et al, Journal of Gastrointestinal Surgery, 2008;12:1738-1744



# RECOMMENDATION FOR BIOLOGICS

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- ▶ For anti-TNF agents, abatacept and tocilizumab
  - ▶ 1 week to 2 months
- ▶ For rituximab
  - ▶ 6 months, or longer until peripheral B cell count is normal
- ▶ According to surgical scenario
  - ▶ holding agent for 2 half-lives if sterile environment (cataract)
  - ▶ holding agent for 5 half-lives if septic environment (colon) or septic risk situation (joint prosthesis)
    - ▶ Royal College of Nursing, 2012



# MEAN HALF-LIVES OF BIOLOGIC AGENTS

	mean half-life	2 half-lives	5 half-lives
etanercept (anti-TNF)	4.3 days	8.6	21.5
adalimumab (anti-TNF)	14	28	70
infliximab (anti-TNF)	8-10	16-20	40-50
golimumab (anti-TNF)	12	24	60
certolizumab (anti-TNF)	14	28	70
rituximab (anti-CD20)	21	42	105
abatacept (selective T-cell costimul blocker)	13	26	65
tocilizumab (anti-IL-6)	13	26	65
anakinra (anti-IL-1)	6 hours	12	60
tofacitinib (janus ass. kinase inhibitor)	3 hours	6	15



# RECOMMENDATION FROM CRA, 2012

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- ▶ Biologic DMARD should be held prior to surgical procedures. The timing for withholding biologic DMARD should be based on the individual patient, the nature of the surgery, and the pharmacokinetic properties of the agent.
- ▶ Biologic DMARD may be restarted postoperatively if there is no evidence of infection and wound healing is satisfactory.
  - ▶ Level II (anti-TNF), IV, Strength C





# RECOMMENDATION FROM OTHER SOCIETIES

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- ▶ American College of Rheumatology
  - ▶ Withhold for more than 1 week
  
- ▶ British Society of Rheumatology
  - ▶ Withhold for 3 to 5 half-lives



# PREDNISONNE

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- One of the highest overall infection rates
  - Smitten, et al, Journal of Rheumatology, 2008;35:387-393
- Bridging patients for which DMARDs and biologics withheld
- Prescribe to avoid adrenal gland insufficiency
  - can occur with equivalent of prednisone 5 mg daily for 4 weeks or 20 mg daily for 5 days...
  - ACTH stimulation test





## QUESTION #4

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- ▶ Would you recommend a steroid stress dose?
  - ▶ 1. Yes, without a doubt
  - ▶ 2. Not sure, most probably
  - ▶ 3. Maybe
  - ▶ 4. No, certainly not!





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# PREDNISONNE AND PREOPERATIVE STRESS DOSE

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- ▶ evidence that usual dosage is enough
  - ▶ 2 small, randomized, double-blind studies
  - ▶ directionally appropriate increase in serum cortisol levels
    - ▶ cortisol level lower
    - ▶ hemodynamic status not affected
- ▶ Thomason et al, Journal of Clinical Periodontology, 1999;26:577-582
- ▶ Glowniak et al, Surgery, 1997;121:123-129
- ▶ Marik et al, Archives of Surgery, 2008;143:1222-1226



# PREOPERATIVE STRESS DOSES

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- Superficial procedures - usual dose, no stress dose
- Minor surgeries (inguinal hernia repair) - 25 mg hydrocortisone or 5 mg methylprednisolone or prednisone day of surgery, then usual dose
- Moderate surgeries (open cholecystectomy, hemicolectomy) - 50-75 mg hydrocortisone or 10-15 mg methylprednisolone day of surgery then taper over 1-2 days to usual dose
- Major surgeries (cardiothoracic, Whipple, liver resection) - 50-100 mg hydrocortisone or 20-30 mg methylprednisolone on day of surgery then taper over 1-2 days to usual dose
  - Adapted from Coursin et al, JAMA 2002;287:236-240



# NSAIDS AND ASPIRIN

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- NSAIDS
  - reversible inhibition of COX-1
  - hold for 4 to 5 half-lives
    - naproxen 12-17 hours
    - indomethacin 7-8 hours
    - diclofenac, ibuprofen 2 hours
  - COX-2 and meloxicam probably safer regarding blood loss
- Aspirin to be held 7 days



# RISK OF THROMBOSIS

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- Presence of antiphospholipid syndrome (APS)
  - surgery, infection and change in anticoagulation can trigger the catastrophic APS
- Assess the need for bridging
  - LMWH
  - do consider risk of bleeding
  - resume anticoagulation postoperatively







## QUESTION #5

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- ▶ What am I missing?
  
- ▶ 1. Nothing
- ▶ 2. One thing, but what?
- ▶ 3. Everything!?





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# RISK OF CERVICAL SPINE INSTABILITY

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- ▶ Anaesthesiologic considerations
  - ▶ Rheumatoid arthritis patients
    - ▶ atlantoaxial subluxation
    - ▶ 80% of patients do have cervical findings, 30% have unsteadiness, sometimes asymptomatic
  - ▶ Ankylosing spondylitis patients
    - ▶ at risk for cervical fracture with minor trauma
    - ▶ atlantoaxial subluxation



# RECOMMENDATION

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- Expert opinion
  - Obtain flexion-extension cervical spine XRay if
    - joint findings
    - cervical pain or findings suggestive of compression (spasticity, spastic gait, ...)



# TAKE-HOME MESSAGES

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- Patients with increased cardiovascular risk
  - to consider as other traditional risk factors?...
- Generally safe to continue conventional DMARDs
- Biologics best withheld prior to surgery
  - but lack of data...
- Lowest possible dose of steroid to be used perioperatively
  - higher risk of infection!
- Highly individualized assessment



# REFERENCES

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