Rheumatology Updates for The General Internist Evidence-based Review

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Disclosure

- I have no financial disclosure of conflicts of interest with the presented material in this presentation .

Learning Objectives

- Laboratory tests in PCP setting
- Describe Treat-to-Target Approach
- Identify new Novel Therapies for Rheumatologic Diseases
- Applying Safety Considerations in Clinical Practice
- Pre-operative Management for patients on Immunosuppressive Therapies
- Vaccinations Recommendations
- Fertility and Medications Safety during Pregnancy

Labs

- Clinical picture is always more important than a test result
- A positive test can suggest a diagnosis but never makes one
- Only order test when CTD is high on the differential

ANA

- **97% of ANA tests ordered did not lead to an autoimmune rheumatic disease diagnosis**, largely due to ordering for nonspecific symptoms.

- Up to **20-30% of healthy individuals** test ANA-positive depending on the assay used.

- Test Method is important
- Best method: **indirect immunofluorescence (IIF) on HEp-2 cells**
- Clinical significance titers are usually 1:160
- Elderly (age >70) have up to 70% low titer + ANA

Pattern of ANA

- Largely replaced by specific serologies
- Refers to the pattern seen on fluorescence
- Provides a clue to the category of the antigen
- Depends on the type of substrate and the experience of the technician
- **Dense fine speckled (DFS) – less likely significant**

Common Pitfalls to Avoid

- Ordering for fatigue alone — low yield, high false-positive rate, leads to unnecessary anxiety and referrals
- Repeating — once positive, it generally stays positive; repeating adds no value
- Equating positive ANA with lupus — most ANA-positive patients do NOT have SLE
- Ignoring a negative ANA — a negative ANA essentially rules out SLE (sensitivity ~98%) but does NOT rule out all autoimmune diseases
- Ordering ENA panel with a negative ANA — generally not indicated unless specifically suspecting Sjögren (anti-SSA)
- Not knowing the lab method — ELISA/multiplex may miss certain patterns

ESR:

- Measurement of the distance in mm that the RBCs fall within a specified tube in 1 hr
- Indirect measurement of acute phase reactant and Ig .
- Acute phase reactants: Fibrinogen, Hapto, CRP, Amyloid A, Ferritin, A1 antitrypsin, IL6 (is a mediator) – decrease neg charge- Rouleaux formation

ESR :

- Pregnancy, DM , ESRD, heart disease, Agining, anemia, female sex, obesity are associated with higher ESR.
- Anything that affects the size of number of RBCs can lower ESR

ESR :

- Marked increased ESR >100 mm/hr
- 35% infection
- 25 % CTD
- 15 % malignancy
- 25 % Other causes

ESR :

- Correct ESR to Age :

Male : Age / 2

Female : (Age + 10) / 2

ESR :

- History , Exam
- Routine – CBC , CMP , UA
- Repeat ESR
- SPEP , UPEP , fibrinogen, CRP
- All ok repeat in 1-3 mo 80% will normalize if no clear S&S.

CRP

- Protein composed of 5 subunits present in all humans plasma
- Thought to activate classical complement pathway
- Elevated in response to cytokine release IL6

- Needs to be corrected to Age and BMI
- Male : Age/50
- Female : (Age+30)/50
- BMI :
- Male : 1 + (BMI-25)/25
- Female : 1 + (BMI-25)/12.5

- Not affected by other IG
- It is a measurement of acute-phase reactants
- Quicker than ESR
- Helps with monitoring response

Arthritis

Gout Management - 2020 ACR Guidelines

- When to treat ?
- Tophaceous gout
- Radiographic damage due to gout
- Frequent gout flares (≥2 per year)
- Consider: First flare with high-risk features (SU ≥9 mg/dL, CKD stage ≥3, urolithiasis)
- Initiating ULT is not recommended in patients with asymptomatic hyperuricemia.

Treatment

- Treatment with allopurinol is the preferred first- line agent
- Testing for the **HLA-B*5801 allele** before starting allopurinol is recommended for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and for African American patients.
- Allopurinol maximum FDA- approved dose is 800 mg/day
- The choice of either allopurinol or febuxostat over probenecid is strongly recommended for patients with moderate- to- severe CKD (stage ≥3)

Treatment

- Administering concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone) is strongly recommended.
- Continuation of prophylaxis for at least 3–6 months after ULT initiation
- Starting ULT **during** the gout flare is preferred over starting ULT after the gout flare
- If therapy is well- tolerated and not burdensome, continue treatment over stopping or tapering down

Treatment

- Switching to an alternative oral ULT agent is recommended for patients taking febuxostat with a history of CVD or a new CVD- related event given the FDA-warning
- Using colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first- line therapy for gout flares over IL- 1 inhibitors or adrenocorticotropic hormone (ACTH) is strongly recommended

Table 7. Management of lifestyle factors*

Recommendation
For patients with gout, regardless of disease activity, we conditionally recommend limiting alcohol intake.
For patients with gout, regardless of disease activity, we conditionally recommend limiting purine intake.
For patients with gout, regardless of disease activity, we conditionally recommend limiting high-fructose corn syrup.
For overweight/obese patients with gout, regardless of disease activity, we conditionally recommend weight loss.
For patients with gout, regardless of disease activity, we conditionally recommend *against* adding vitamin C supplementation.

Treatment

- Switch hydrochlorothiazide to an alternate antihypertensive when feasible
- Choosing losartan preferentially as an antihypertensive agent when feasible
- Don’t Stop low- dose aspirin

Rheumatoid Arthritis

Why talking about RA ?

- Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis. 1 % of the population .

- Uncontrolled inflammation may have other health risks, including higher rates of cardiovascular disease and osteoporosis.

- Early and effective therapy is important to achieve optimal outcomes.

What is RA ?

- Chronic
- Systemic
- Inflammatory disorder
- Has a pattern of joint involvement
- Serum: autoantibodies that include rheumatoid factor (RF) and antibodies to citrullinated protein/peptide antigens (ACPA).
- The primary site of pathology is the **synovium of the joints**.

RA Auto-Antibodies

- **Anti-Citrullinated Protein Antibodies (ACPA/Anti-CCP):**
- Highest specificity for RA (>98% when using anti-CCP2 assay)
- Sensitivity: 60-74% depending on assay
- Can be detected years before clinical disease onset (median 4.5 years)
- Associated with more aggressive joint disease, radiographic progression, and ILD
- **Rheumatoid Factor (RF):**
- Lower specificity than ACPA
- Higher sensitivity: IgM-RF detected in ~65% of RA patients
- **Can be present in other conditions and healthy elderly individuals**
- **Other Autoantibodies: when combined, have high specificity and sensitivity**
- Anti-carbamylated protein (anti-CarP) antibodies
- Peptidyl arginine deiminase-4 (PAD4) antibodies
- Anti-RA33 antibodies
- Collagen type 2 antibodies
- Protein 14-3-3η

RA- Treatment

- Treat to Target Approach
- Start DMARDs immediately upon diagnosis
- Follow-up every 1-3 months
- Target: Remission or low disease activity by 6 months

RA- Treatment

- **First-Line Therapy:**
- Methotrexate monotherapy for moderate-to-high disease activity
- Start 10-15 mg/week, titrate to 25 mg/week
- **Inadequate Response to Methotrexate:**
- Add biologic DMARD (TNF inhibitor, IL-6 inhibitor, abatacept) OR
- Add targeted synthetic DMARD (JAK inhibitor) OR
- Switch to an alternative conventional synthetic DMARD

Labs

- Infections to Screen for: Hepatitis B, C (don't forget to add HepB core total). Can add TB, HIV, Syphilis
- Get a baseline **CXR before starting**
- Counseling on Pregnancy Prevention while on MTX
- Prescribe weekly with Daily Folic Acid
- Check CBC, BMP and LFT 1 month after initiation of therapy

RA-Treatment

- **Glucocorticoid Strategy:**
- Use as "bridging therapy" **only**
- Taper to ≤5 mg/day prednisone equivalent
- Goal: Complete withdrawal

JAK Inhibitors - Efficacy Safety Warnings

- Tofacitinib (Xeljanz) - pan-JAK inhibitor
- Upadacitinib (Rinvoq) - JAK1-selective
- Baricitinib (Olumiant) - JAK1/2 inhibitor

- **Advantages:**
- **Oral** administration
- **Rapid** onset of action
- Superior efficacy to methotrexate monotherapy
- Effective after TNF inhibitor failure
- **FDA Boxed Warnings (2022):**

Based on ORAL Surveillance trial in patients ≥50 years with ≥1 CV risk factor:

- Increased major adverse cardiovascular events (HR 1.33 vs TNF inhibitors)
- Increased malignancy risk (HR 1.48 vs TNF inhibitors)
- Increased venous thromboembolism
- Increased mortality

Refer to Rheumatology

- Inadequate response to methotrexate after 3 months at therapeutic dose
- Need for biologic or JAK inhibitor therapy
- Unclear diagnosis or atypical presentation
- Extra-articular manifestations (interstitial lung disease, vasculitis, eye..)

Axial Spondyloarthritis – 2019 ACR Guidelines

- Few Points
- This is a spectrum of Conditions with Multiple associations
- Ankylosing Spondylitis
- Psoriatic Arthritis
- IBD-arthropathy
- Eye Inflammatory Disease
- Skin Disease (Psoriasis)
- Peripheral Disease (Enthesitis, Dactylitis, Nail)

Feature	Inflammatory Back Pain	Mechanical Back Pain
Age of onset	40-45 years	Any age
Onset	Insidious/gradual	Often acute, may follow trauma
Morning stiffness	≥30 minutes, improves with activity	Brief (30 min) or absent
Effect of exercise	Improves pain	May worsen pain
Effect of rest	Worsens pain/stiffness	Improves pain
Nocturnal pain	Second half of night; awakens patient	Uncommon
Response to NSAIDs	Good (often dramatic)	Variable
Duration	Chronic (>3 months), persistent	Variable, often episodic

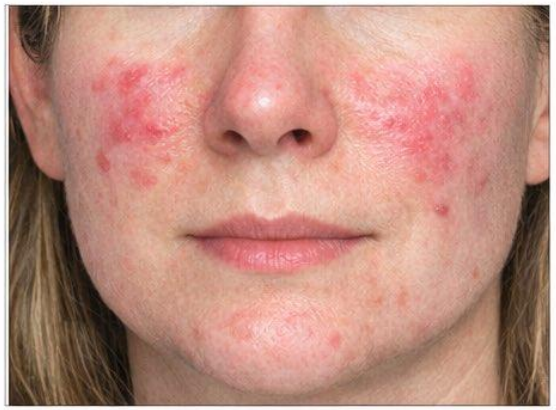
Major Therapeutic Advances :

- **TNFi**
- **IL-17 Inhibitors**
- **JAK Inhibitors**
- **IL-12/23 Inhibitors**

SLE

- ANA is positive 1:80
- **Inflammatory** joint pain/swelling (morning stiffness >30 min, swelling, symmetric, deformities)
- Photosensitive or malar rash (not rosacea)
- Unexplained cytopenias (WBC <4,000, platelets <100,000, HA)
- Proteinuria or active urine sediment
- Raynaud phenomenon (digital pitting, ulcers, or **puffy fingers**)
- Recurrent Oral/nasal ulcers
- Serositis (pleuritis, pericarditis) – Echo , Imaging
- Dry eyes/dry mouth (sicca symptoms) – significant

Rosacea

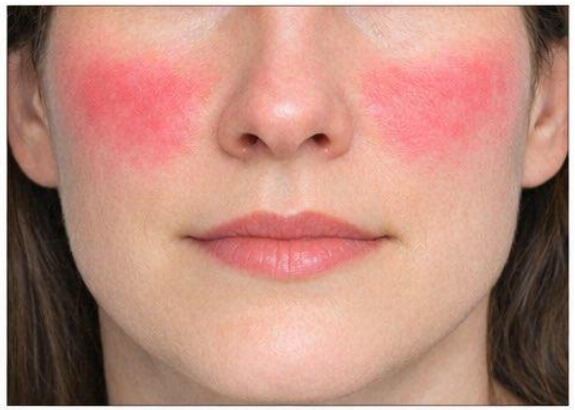


Rosacea

Characteristics

- Chronic redness in the centrofacial area
- Papules, pustules, phymatous changes
- Telangiectasias

Malar Erythema



Malar Erythema

Characteristics

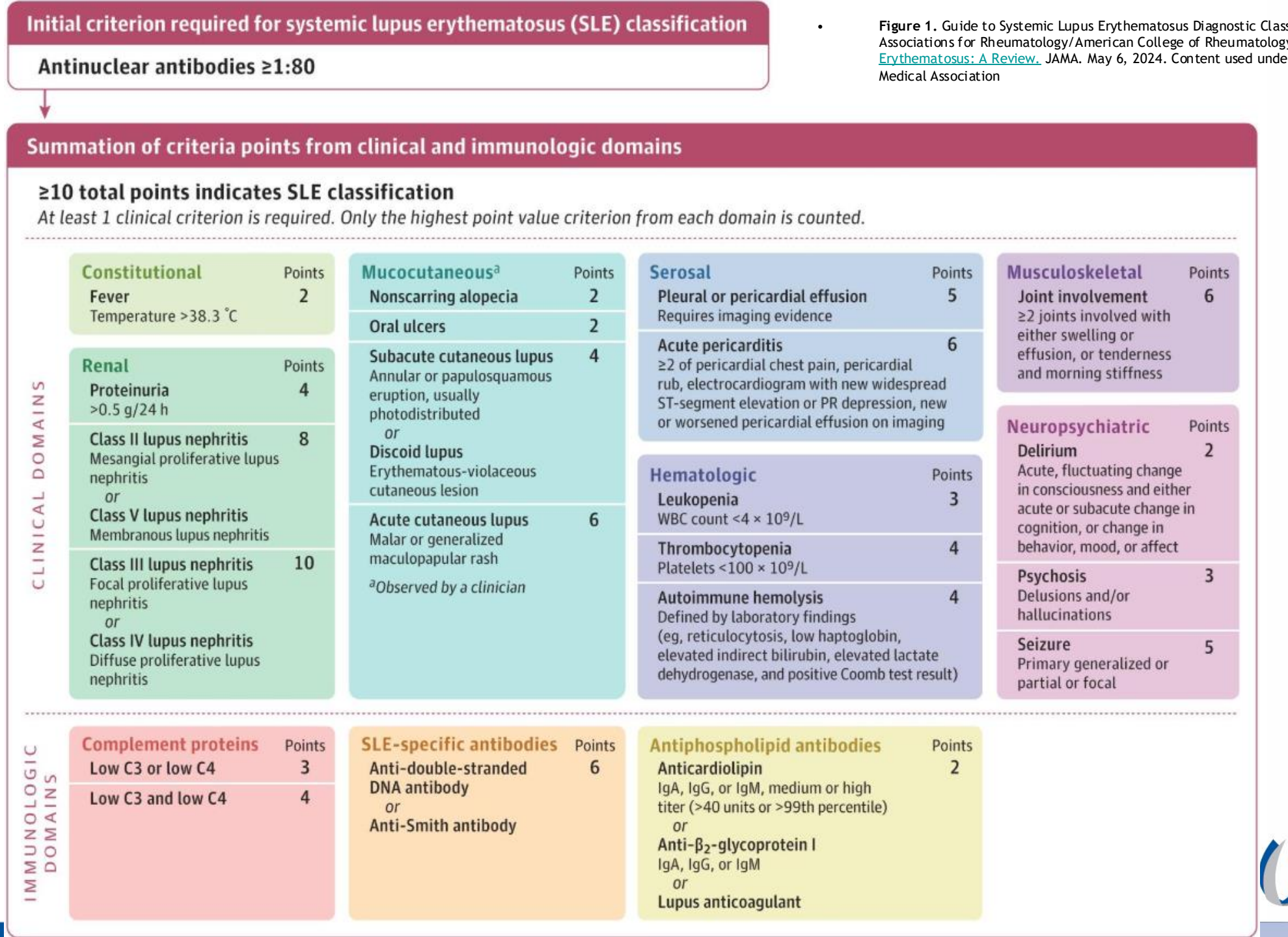
- Malar (butterfly) distribution
- Symmetrical, sharply demarcated redness
- Smooth, non-pustular rash

Note: Consider lupus when there is a malar rash, photosensitivity, and systemic symptoms.

Adapted from ROSCO 2018 & EULAR/ACR 2019

X: @wallacin_

- Baseline Labs :
- CBC, BMP , LFTs , UA with UPCr , C3, C4
- ENAs : Smith , RNP, SSA, SSB, dsDNA
- Some labs add : Scl70 and Jo-1



- **Figure 1.** Guide to Systemic Lupus Erythematosus Diagnostic Classification Adapted From 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology Classification Criteria Systemic Lupus Erythematosus: A Review. JAMA. May 6, 2024. Content used under license from the JAMA Network® © American Medical Association

Systemic Lupus Erythematosus 2025 Updates

- **Hydroxychloroquine** should be standard therapy for **all** people with SLE unless contraindicated.
- Glucocorticoids should be used primarily for initial control of inflammation and flare-ups, with tapering as soon as possible.
- Early introduction of immunosuppressive therapies (conventional and/or biologic) for ongoing SLE activity is encouraged to achieve control of SLE inflammation .

Hydroxychloroquine

- In people with SLE receiving HCQ therapy, we conditionally recommend a long-term average daily HCQ dose goal of ≤5 mg/kg over a dose goal of >5 mg/kg to minimize retinal toxicity

Belimumab (Benlysta):

- Now recommended for both extrarenal SLE AND lupus nephritis
- Add-on therapy to the standard of care
- Available in SubQ and infusion Formulation

Anifrolumab (Saphnelo):

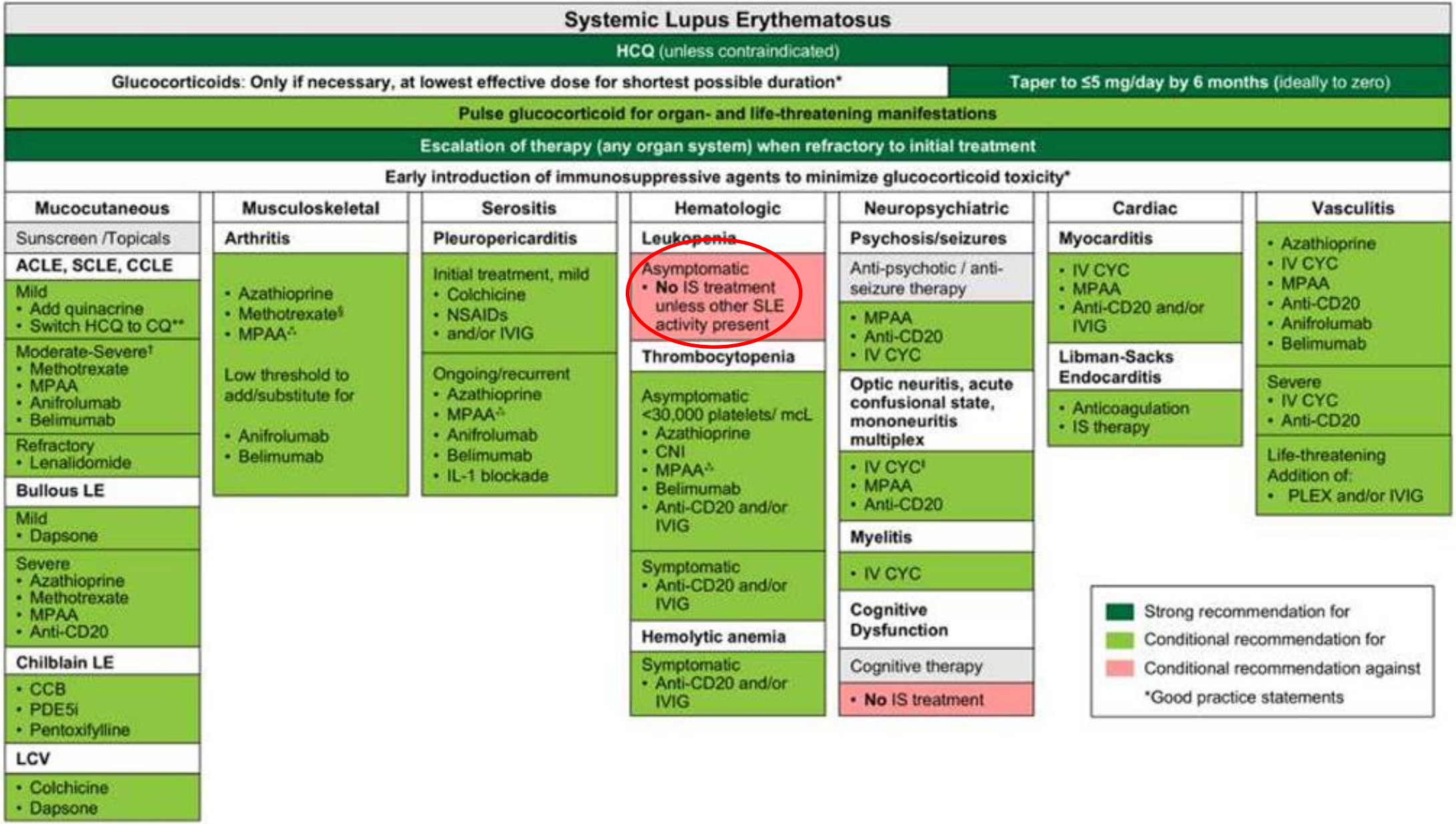
- Type 1 interferon receptor inhibitor
- For moderate-to-severe extrarenal SLE
- Monthly infusion
- Works well for patients with Cutaneous Features

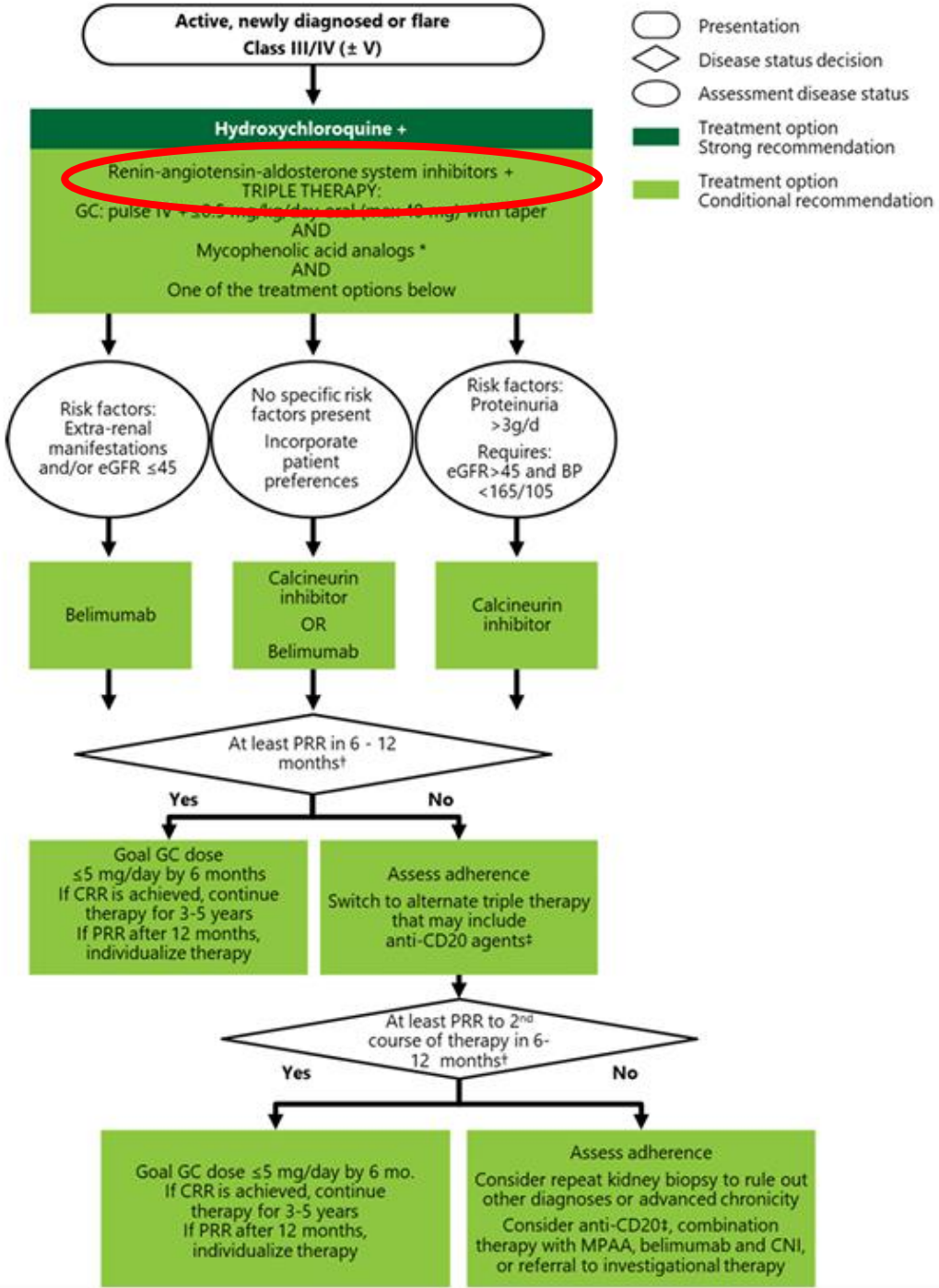
Voclosporin (Lupkynis):

- Novel calcineurin inhibitor
- For lupus nephritis in combination with mycophenolate
- Superior response rates vs. mycophenolate alone (AURORA 1 study)
- Works well in high UPCr patients

Obinutuzumab

- **Anti-CD20 monoclonal antibody**
- Causes more profound and sustained B-cell depletion than rituximab





Glucocorticoid-Induced Osteoporosis - 2022 ACR Guidelines

- **Who to Assess:**

Adults beginning or continuing ≥2.5 mg/day prednisone for >3 months

- **Initial Assessment :**

Clinical fracture assessment

BMD with vertebral fracture assessment (VFA) or spinal x-ray

FRAX (if ≥40 years old)

- **Risk Stratification:**
- **Medium Risk:** No recent fracture
- **High Risk:** Recent fracture (within 2 years) and/or ≥1 vertebral fracture (grade ≥2)
- **Very High Risk:** Age ≥70 years with recent hip/pelvis fracture and/or ≥1 vertebral fracture

- **Medium Risk:** Oral or IV bisphosphonates
- **High Risk:**
- Oral/IV bisphosphonates, denosumab, or PTH/PTHrP analogs
- Anabolic agents (PTH/PTHrP) are recommended over antiresorptive
- **Very High Risk:**
- Anabolic agents (Teriparatide, Romosozumab) are recommended as initial therapy

- **Key Considerations:**
- All patients: Optimize calcium and vitamin D
- Sequential therapy required after denosumab, romosozumab, or PTH/PTHrP

Perioperative Medication Management 2022 ACR/AAHKS Guidelines for Elective Total Hip/Knee Arthroplasty

- **Continue Through Surgery:**
- Methotrexate
- Leflunomide
- Hydroxychloroquine
- Sulfasalazine
- Apremilast

- **Biologics:**
- Plan surgery after next dose is due (~1 dosing interval)
- Example: Adalimumab (every 2 weeks) → surgery at week 3
- Example: Rituximab (every 6 months) → surgery during month 7

- **Special Considerations for SLE:**
- Non-severe SLE: Withhold mycophenolate, azathioprine, cyclosporine, tacrolimus 1 week prior
- Severe SLE: Continue immunosuppression through surgery

- Balance infection risk vs. disease flare risk through shared decision-making

- In Patients with RA or SLE consider Cardiopulmonary clearance for Pre-op optimization

Vaccinations – 2022 ACR guidelines

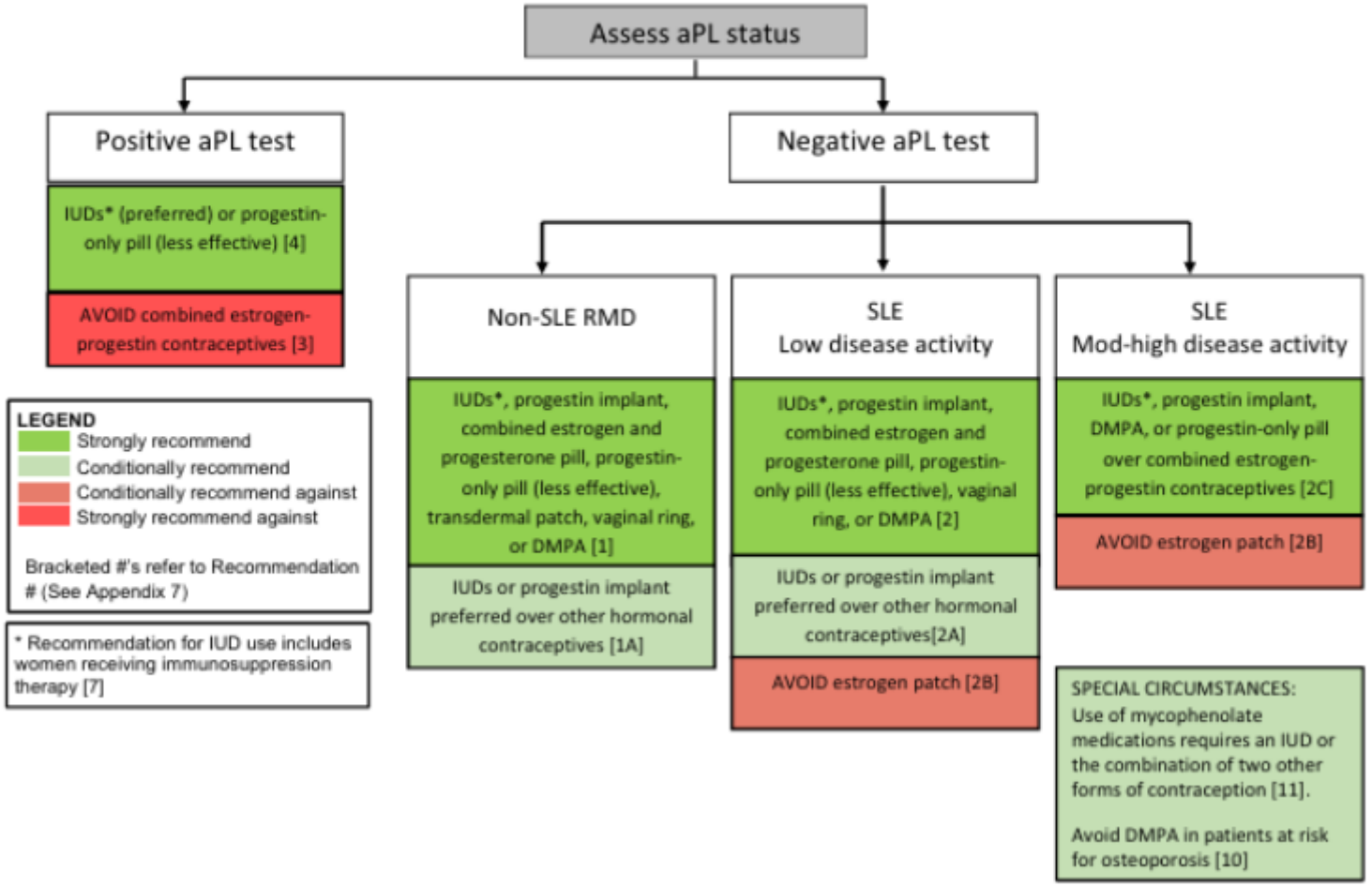
- For patients aged ≥ 65 years, patients aged >18 and <65 years give **high-dose** influenza vaccination
- For patients aged <65 years give **pneumococcal vaccination**
- For patients aged >18 years give **recombinant zoster vaccine**
- For patients aged **26 - 45** years not previously vaccinated, give **HPV vaccine**

- Giving **multiple** vaccinations on the same day rather than giving each vaccination on a different day is recommended.
- Would recommend **deferring live-attenuated** vaccines.

	Influenza vaccination	Other non-live attenuated vaccinations
Methotrexate	Hold methotrexate for 2 weeks *after* vaccination*	Continue methotrexate
Rituximab	Continue rituximab**	Time vaccination for when the next rituximab dose is due, and then hold rituximab for at least 2 weeks after vaccination
Immunosuppressive medications other than methotrexate and rituximab	Continue immunosuppressive medication	Continue immunosuppressive medication

Reproductive Health - Preconception Planning – 2020 ACR Guidelines

Discuss contraception and pregnancy planning at initial or early visit with women of reproductive age and counsel regarding efficacy and safety [GPS]. Recommend barrier methods if more effective methods are contraindicated [GPS]. Recommend emergency (post-coital) contraception when necessary [6].



- **Essential Preconception Strategy:**
- Achieve remission or low disease activity for several months on pregnancy-compatible medications
- Well-controlled disease before pregnancy: 10% flare rate during pregnancy

- **Medications Compatible with Pregnancy:**
- **Synthetic DMARDs:**
- Hydroxychloroquine
- Azathioprine
- Sulfasalazine
- Colchicine
- Cyclosporine
- Tacrolimus
- **Biologics:**
- All TNF inhibitors can be used throughout pregnancy
- Certolizumab: Minimal placental transfer (strongly recommended to continue)
- Other TNF inhibitors: May discontinue in the third trimester
- **Glucocorticoids:**
- Nonfluorinated forms are acceptable
- Keep ≤10 mg/day prednisone equivalent

- **MUST Discontinue Before Conception:**
- Methotrexate (proven teratogen)
- Mycophenolate mofetil/mycophenolic acid (proven teratogen)
- Cyclophosphamide (proven teratogen)
- Leflunomide (requires cholestyramine washout if detectable levels)

- **SLE-Specific Recommendations:**
- **Essential Medications:**
- Hydroxychloroquine: Continue
- Low-dose aspirin: Start at the end of the first trimester to reduce pre-eclampsia risk
- **Antiphospholipid Syndrome:**
- Anticoagulant therapy required throughout pregnancy
- **Anti-Ro/SSA or Anti-La/SSB Antibodies:**
- Increased risk of congenital heart block in offspring (HCQ)
- Requires additional fetal monitoring

Biosimilars:

- Increase accessibility
- Reduce costs
- Equivalent efficacy and safety to originators

Questions

- Thank you ..