**PHARMVIGNETTE RHEUM/IMMUNE**

**CC: "I have a rash, I'm so tired, and my joints ache"**

**HISTORY OF PRESENT ILLNESS:** Tabatha, a 38-year-old female patient, presents to the NP clinic complaining of a rash x 2 weeks. She reports that appears on her nose and cheeks and gets more pronounced when she is out in the sun. She reports it is painful and itchy at times. She also noticed that her hair has been falling out in patches. Other complaints include fatigue, and she needs at least one nap a day, usually in the afternoon. Initially she thought it was because she is a mother of 2 busy toddlers. She has some mild aches in her fingers and elbows, but she attributes it to "getting older". Her medical history is noncontributory as she has never been ill before but gets occasional aches and pains and heartburn. She medicates for these maladies by taking an occasional ibuprofen and antacid. She has no other prescription or OTC medications or supplements. She does not smoke or drink ETOH (never). Other ROS reveals a 10 lb. weight loss over the past few months (unintentional), some mild chest pains (these are intermittent and last for a few minutes), and a "little" shortness of breath (also intermittent and only last for a few minutes).

**MEDICATIONS**: OTC ibuprofen and antacids (TUMS ®) as needed -not often, once, or twice every few months. **Allergies**: none

**PMHX:** undiagnosed joint pains prior to today's visit (played sports in high school), undiagnosed heartburn after certain foods (when she eats Mexican-style foods). G2P2, no complications w/ either pregnancy. Breastfed both infants x 1 year. Age of pregnancies 35, 37 -genetic testing performed and no issues.

**SOCIAL HX:** married, stay at home mother of 2 toddlers at home; nonsmoker, nondrinker, no illicit drugs. Went to college and has a Bachelor of Science in chemistry. Exercises as she can fit it in with 2 toddlers. Eats very healthy-almost "vegan" and organic foods only, adds occasional chicken or fish (1-2 times week). Drinks only water and caffeine intake is through tea-low, only one tea per day.

**FAMILY HX:** denies any known genetic issues in the family. MGM (66) alive, hypothyroidism; MGF (70) CHF, HTN, HLD; PGM (76) HTN, HLD, AFIB; PGF (DEC) pancreatic cancer, hyperthyroidism

**PHYSICAL EXAM**: VS: BP 112/70 HR: 79 RR 19/unlabored temp 37.8*

**CONSTITUTIONAL**: Well nourished, well-developed American Indian female with NAD. Appears tired and weak.

**HEENT:** PEERLA, EOM, no obvious papilledema, +anterior and posterior cervical lymphadenopathy; no thyromegaly, no sinus tenderness on maxillary sinuses B/L; no lesions or exudate

**SKIN:** rash noted on nasal bridge and cheeks; none on nasolabial folds; no other lesions or rashes noted on external skin.

**CHEST:** RRR s1s2 no MGR, no pericardial friction rub.

**RESP:** Lungs CTA, non-labored w/ equal chest rise.

**ABDOMEN:** NT/ND, BSX4 no palpable mass or organomegaly, no adiposity.

**NEUROLOGIC:** AAOx4, CNII-XII intact. Strength B/L U/L 5/5; DTR +2 symmetric no gait disturbance, heel to shin with no difficulty

**PSYCHE:** affect normal, interactive with good eye contact.

**LABS/IMAGING:**

MRI brain negative (no lesions, masses, or areas of infarct)

CRP 30; ESR 25; ANA 900:1 homogenous pattern, smith antigen +; U/A +proteinuria

**DIAGNOSIS IS:** SYSTEMIC LUPUS ERYTHEMOUS

After you have read and interpreted the case, review the case, and see if it "makes sense" to you. The diagnosis is given to you but there may be clues you need to recognize so you are able to "prescribe" the medicine. The focus now is to answer questions about how you would prescribe medication and everything that entails.

**QUESTION 1**. Look up SLE (Emedicine ®, Epocrates ®, Up to date ®, etc.) and determine what the EBP pharmacotherapeutic plan would be using the information from the presentation above. Write it out and how you would prescribe based on the presentation above. You are prescribing for a naïve patient that has never had lupus prior to you seeing them (the pharmvignette).

**QUESTION 2**. Understanding the severity of an illness is paramount to understanding the plan. Based on the information above, would you classify this patient as having a mild, moderate, or severe presentation of SLE? How do you determine this, what parameters help determine severity?

**QUESTION 3**. What are the GOT (goals of treatment) for SLE? Please list all.

**QUESTION 4.** What is the role of the NP versus the specialist in this scenario? Even though the specialist may prescribe the medicine, what is your responsibility as the PCP?

**QUESTION 5**. Choose one of the medications and determine (1) what do you need to know before you write the script? (2) what absolute contraindications are there? (3) what ADRs are present (choose the top 5 common and the top 5 severe)?

**ANSWERS AND RATIONALE W/ MEI SHEET (MINIMAL EXPECTED INFORMATION) FOR SYSTEMIC LUPUS ERYTHEMOUS PHARMVIGNETTE ARE ON THE NEXT PAGES.**

**QUESTION 1. Look up SLE (Emedicine ®, Epocrates ®, Up to date ®, etc.) and determine what the EBP pharmacotherapeutic plan would be using the information from the presentation above. Write it out and how you would prescribe based on the presentation above. You are prescribing for a naïve patient that has never had lupus prior to you seeing them.**

For this patient who is a female, aged 15 to 50 years old, and presents with fever, arthralgias and malar Rash and has associated findings (esp. nephritis), she would benefit from an admission to the hospital for acute flair management and further workup. Per the pharmvignette, this patient has a photosensitive malar rash (skin/cutaneous finding) fatigue (systemic), low grade fever (systemic), alopecia (cutaneous), joint aches and pains (myalgias), unintentional weight loss of 10 lbs. (4.5kg) (systemic), chest pains (pleuritic or CV?), and shortness of breath (pleuritic or CV). Based on your diagnostic criteria you must have a ++ ANA and clinical symptoms. Both of these are present. You can confirm the diagnosis of SLE here. She has mainly mucocutaneous s/sx which are consistent with milder disease by her symptomology, however her biochemical findings give rise to kidney involvement with proteinuria present. Since we have kidney involvement, more workup needs to commence, but based on the information given without inference of pending labs, mild to moderate disease presentation would be an appropriate starting point with close f/u and pending laboratory and biopsy (kidney) findings or potential lupus nephritis. Based on the treatment plan after determining diagnostic level, prescribing HCQ would be appropriate. Also, high dose steroids or methylprednisolone for her acute flair.

In the hospital, patient would be placed on high dose steroids and IV cytotoxic agents (mycophenolate or cyclophosphamide) due to possible lupus nephritis.

After return home from acute hospitalization patient would start Hydroxychloroquine 200 mg once daily to start. Up to 400 gm daily in 2 divided doses for max therapy. She would be placed on NSAIDS for arthralgias. She would need topical steroids or topical calcineurin inhibitors, in addition to the HCQ. If her workup for lupus nephritis is positive, she will mycophenolate or cyclophosphamide.

**QUESTION 2. Understanding the severity of an illness is paramount to understanding the plan. Based on the information above, would you classify this patient as having a mild, moderate, or severe presentation of SLE? How do you determine this, what parameters help determine severity?**

She has mainly mucocutaneous s/sx which are consistent with milder disease by her symptomology, however her biochemical findings give rise to kidney involvement with proteinuria present. Since we have kidney involvement, more workup needs to commence to really classify her, but based on the information given without inference of pending labs, moderate disease presentation would be an appropriate starting point. She also qualifies for acute hospitalization due to the constellation of symptoms that are present, due to this she moves into the severe category.

**QUESTION 3. What are the GOT (goals of treatment) for SLE? Please list all.**

Tools used for standardized assessment of presenting signs and symptoms. Then eval from disease activity standpoint and patient complaints. Based on QOL (quality of life), fatigue

reduction, pain reduction as your goals, prescribe medications to fit your patient presentation. Also use a Quantifiable symptom reduction (choose & use a tool).

1. ****Remission- no clinical activity, no use of medications (immunosuppressants or glucocorticoids)

2. Partial renal remission- greater than 50% reduction in proteinuria to sub nephrotic levels and serum creatinine within 10% from baseline

3. Complete renal remission- proteinuria <500 mg per 24 hours and serum creatinine within 10% from baseline

4. **Low disease activity- SLEDAI score <3 on anti-malarial Rx OR SLEDAI <4 on glucocorticoids dose 7.5 mg or less and well-tolerated immunosuppressants

**QUESTION 4. What is the role of the NP versus the specialist in this scenario? Even though the specialist may prescribe the medicine, what is your responsibility as the PCP? (think prescribing DMARDS and immunosuppressant agents)**

Patients taking these medications will be managed by a rheumatologist, but as the PCP NP there are certain things to be aware of related to PMHX, ADRs and possible medication interactions. (1) All patients taking immunosuppressants or DMARDS (disease modifiable anti-rheumatic drugs) will need certain blood work routinely, and also prior to prescribing the biologic agents. As a PCP NP, you could order this workup before the patient gets the rheumatologist. (2) There are pertinent medical concerns needing evaluation prior to the initial prescription of any DMARDS or immunosuppressant agents. This should be a part of your history after you get an idea this may be a rheumatologic concern, as many of their diseases use DMARDS. (3) An astute NP and a collaborator with interdisciplinary collaboration foresight will have these items completed prior to the patient going to the specialist.

(1a) The blood tests prior to the initiation of the DMARDS are CBC w/ diff, LFTs, Kidney function, lipids, serology TB, Hep B and C. Pregnancy test if applicable. After starting the drugs, you should get CBC w/ diff, LFTs, Kidney function, lipids, serology TB, Hep B and C testing routinely, such as every 1-2 months, however this is at the discretion of the practitioner. Concerns related to biologic and nonbiologic DMARDs include increased CV risk, liver & hematologic toxicity, renal impairment, infection, and bleeding.

(2a)there are certain medical history concerns and this needs to be completed prior to prescribing the biologic agent >>> allergy to rubber or latex; are you taking any other immunosuppressant medications; are you prone to frequent infections; any history of hepatitis B, uncontrolled diabetes, HIV, TB, CHF, skin issues, other autoimmune diseases; and have you ever been exposed to chicken pox, measles, mumps, or rubella.

**QUESTION 5. Choose one of the medications and determine (1) what do you need to know before you write the script? (2) what absolute contraindications are there? (3) what ADRs are present (choose the top 5 common and the top 5 severe)?**

**Since hydroxychloroquine is needed for every patient with SLE, we will take a deep dive into this medication. HCQ – Plaquenil. A well tolerated anti-malaria agent with immunomodulator effects that reduces overall dz flares (20-40%), reduces accrued damage, and is a cornerstone in management. It also reduces kidney progression. Tolerable ADR panel.**

**1. MOA- unsure of all activity made by drug but can pass through cell membrane into the lysosomes where it disrupts key cellular activity (inhibits TLR of the cGAS-STING pathway which limits enzyme and cytokine release, receptor recycling, antigen presenting, T cell polarization, and NK activation. It also increases protection against UVA and UVB light).**

**2. Monitor vision mainly; educate the patient on using an AMSLER grid every 2 weeks. Report any vision changes immediately to the clinic.**

**3. SPEC-POPS. (a) Crosses placenta and is equal concentration between mother/fetus. (b) Able to be used in pregnancy and breastfeeding. (c) Reduces neonatal lupus or heart block (from circulating SS-A/B antibodies).**

**4. There can be heart effects including prolonged QT with importance of not combining medications that may prolong further, such as macrolide azithromycin and tamoxifen.**

**5. Should be greater than 18 years old for indication of SLE. Take the drug with a meal or a glass of milk .**

**6. Recommended dosing is 200 to 400 milligrams per day which can be in one or two doses. Most common side effects include rash pigment changes and diarrhea.**

**DISEASE MONOGRAPH**

1) SLE (SYSTEMIC LUPUS ERYTHEMATOUS)

i) **Define:** Chronic systemic autoimmune dz characterized by fatigue, rash, and joints pains that often affects females of childbearing age and is an illness that waxes and wanes

ii) **Core Concepts**: antigen-driven immune-mediated disease
   a. characterized by: IgG antibodies to double-stranded (ds) DNA & nuclear proteins
   b. Type III hypersensitivity reaction
   c. 5-yr survival is >90%
   d. renal failure, infection, and accelerated cv dz are often cause of death
   e. long term medication needed to manage dz processes and symptoms

iii) **Pathogenesis**: The exact pathogenesis is unknown however theories about how this autoimmune disease include the following advanced understanding: autoimmunity that creates autoantibodies (antibodies targeting self) which cause a defect in apoptosis >>> that causes increased cell death = disturbance in immune tolerance/loss of tolerance (how we get the autoimmune mechanism  both central or peripheral tolerance is lost, there are self-reactive lymphocytes [Central tolerance/thymus = t-cell apoptosis and bone marrow (BM) regulatory T cells]. Peripheral tolerance leads to anergy, or apoptosis of T/B cells). Next, dysregulated lymphocytes target intracellular antigens in the form of nucleosomes. There is defective clearance of the cellular debris (from apoptosis) which

allows for persistent antigen presence. Also, there is immune complex production (IgG) in the microvasculature which gets deposited in many tissues, mainly skin and kidney basement membranes. There are defects in both signaling and effector function of the T cells and result in secreting less interleukin IL-2 and there are changes in the CD3 signaling subunits, CD8 cytotoxicity; T-regulatory, B-cell help; migration; and adhesion. There is consistent and prolonged complement activation and inflammation in many parts of the body. In active SLE, this process has been confirmed by demonstration of complexes of nuclear antigens such as DNA (=dsDNA), immunoglobulins, and complement proteins (C3, C4, CH50) at these sites.

**iv) Etiology**

a. Unknown. Theories include
    i. hormonal factors. Estrogen? Women of childbearing age are impacted greatly 12;1 ratio, then at menopause ratio drops significantly and becomes almost equal. There is something about access of the body to estrogen that increases the risk.
    ii. Drugs. See list below for specifics.
    iii. Noninfectious/environmental. UV light exposure
    iv. Infectious. Viruses EBV
    v. Genetics. HLA (human leukocyte antigen) system.

**v) Risk factors**

a. Exposure to EBV, enterococcus gallinarum
b. Vitamin D def. pregnancy, silica dust, cigarette smoking, estrogen use in PMP (postmenopausal patient)
c. PROTECTIVE: breastfeeding,

**vi) Epidemiology**

a. Ages 15-45; 12: 1 female to male; after 45 y/o 2:1 ratio
b. >90% of cases occur in females-at childbearing age
c. Age of onset usually around 20-30 years (20% dx at these ages)
d. 1.5 million cases. Pooled prevalence per 72.8/100000 (five national lupus registries funded by the Centers for Disease Control and Prevention (CDC)
    i. ??overdiagnosis in US??
e. incidence estimates at roughly 5.1 per 100,000 person-years (95% CI 4.6 to 5.6) (five national lupus registries funded by the Centers for Disease Control and Prevention (CDC)
f. Ethnicity: Indigenous/Alaskan natives >>Hispanic >> Black >> Asian/ White
    i. Severity of disease increases in Black and Asian descent

**vii) S/Sx (signs and symptoms *** classic presentation)**

a. Method: SLE has many s/sx, so an understanding of the clinical presentation is paramount to diagnosing the condition. The clinician should be familiar w/ the diagnostic criteria (EULAR/ACR 2019) and recognize target organ damage for

classification of this complex disease. If a patient is C/O (complains of) at least 2 of these symptoms, then a workup is appropriate, ANA, and basic labs to prove any other possibilities (add to your differential possibilities). SLICC criteria (2012-Systemic lupus International Collaborating Clinics) was released to improve upon already existing ACR 1997 classification criteria. SLICC added criteria of neurologic manifestations, relevant immune results, cutaneous manifestations, despite biopsy conformed nephritis a person could still fail ACR criteria.

b. **Behind the individual labs and clinical presentation there will be numbers in parentheses which are the weighted items from the EULAR/ACR 2019 criteria that will get you the diagnosis.**
    i. ***(Malar rash (6)- characterized by erythema over the cheeks and nasal bridge >> but sparing the nasolabial folds), or Discoid rash (4) (in sun-exposed areas but are plaque like in character, with follicular plugging and scarring.) w/ Photosensitivity (can be acute or chronic-may last 2 days).
    ii. Fatigue, wt. loss or wt. changes, Fevers >38.3*C or 101*F (2)*** , lymphadenopathy may be found.
    iii. Joint pain (6)*** (arthralgias), muscle pain (myalgias) or arthritic pain (small joints of the hands, wrists, and knees (usually symmetrical, polyarticular). AVN (avascular necrosis seen in 44% of SLE R/T high dose steroid use)
    iv. Alopecia (2) is a patchy pattern of hair loss or present in temporal regions and is non scarring.
    v. Mucocutaneous: Oral ulcers (2), any mucocutaneous manifestations (Raynaud phenomenon, Livedo reticularis, Panniculitis (lupus profundus), Bullous lesions, Vasculitic purpura, Telangiectasias, Urticaria
    vi. Raynaud's' pleuritis, sicca (Sjogren's syndrome-dry mouth and dry eyes)
    vii. Kidney^^^ (proteinuria (4), screat, urinary casts) most common visceral organ involved. +glomerular dz within 1 year, AKI and CKD may present with uremia and fluid overload. HTN or hematuria (think lupus nephritis); Edema (periorbital or peripheral regions), anasarca, and morning presacral edema upon arising from bed. Renal biopsy (8) lupus nephritis (mild to moderate) or renal biopsy lupus nephritis severe (10)
    viii. Neuropsychiatric -seizures (5) and psychosis (3) but also may include Acute confusional state, Delerium (2), acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome), Anxiety disorder, Aseptic meningitis, Autonomic disorder, Cerebrovascular disease, Cognitive dysfunction, Cranial neuropathy, Demyelinating syndrome, HA, Mononeuropathy (single/multiplex), Mood disorders, Movement disorder (chorea), Myasthenia gravis, Myelopathy/Plexopathy, Polyneuropathy
    ix. Pulmonary manifestations (lupus serositis)- pleurisy, pleural effusion (5), pneumonitis, pulmonary hypertension, and interstitial lung disease.
    x. Gastrointestinal- infectious causes (bacterial, viral [CMV]), nausea and dyspepsia
    xi. Cardiac (lupus serositis) - pericarditis (6), pericardial effusion (5), vasculitis, myocarditis, heart failure, angina, CAD, antiphospholipid syndrome

xii. Hematologic- leukopenia (3), lymphopenia, anemia, or thrombocytopenia (4), medication-related cytopenias. Immunosuppression may predispose persons with SLE to frequent infections. Autoimmune hemolysis (4) or hemolytic anemia (4)

**viii) Workup**

a. Method: If a patient has C/O at least 2 of these symptoms, then a workup is appropriate, ANA is first initial testing ALONE, then if positive move on to basic labs to prove any other possibilities (add to your differential possibilities) and work up the rheum or connective tissue disorder. *NP POV: if your patient is complaining of something work it up, you have a differential for a reason. If fatigue is a main complaint, that has such a wide etiology, so do not wait for a +ANA then do basics. Maybe they have anemia, or any of the other DDX, you could start working that up too. Do not go crazy as you need a reason to order labs, but within reason work it up.*

i. Labs

1. CBC w/ diff (rule out anemia, eval for cytopenias)
2. ESR, CRP (assess for inflammation-non-specific, if both severely elevated consider infectious process) ESR lags behind CRP-more of an acute phase reactant than ESR
3. U/A(eval kidney), CMP-BUN/electrolyte/LFTs, spot protein/creatinine ratio, CKs, TSH (R/O thyroid); BC x2 (R/O endocarditis)
4. PTT/Coags (check liver function and possible eval for Anti-phospholipid syndrome)
5. Complement levels -C3, C4, CH50, (Low C3 OR low C4-3pts) (Low C3 AND Low C4 -4pts). ANA (<1:320 is possible in normal population and non-specific, positive if >80:1 usually homogenous pattern), dsDNA antibody (6) (normal titre is 1:1 and correlates w/ disease activity), anti-Smith antibody (6); Anticardiolipin Antibody (2), Anti-ribonucleoprotein (Anti-RNP); Anti-Beta2-Glycoprotein1; Direct Coombs; RF and anticyclic citrullinated (anti-CCP R/O RA)
6. Lyme serology, HIV serology (R/O DDX)

ii. Imaging/testing includes:

1. ECG: R/O carditis
2. X-rays-joints (little evidence of SLE); Chest Xray (assess for pleural effusion, PE, alveolar hemorrhage; monitor interstitial lung dz)
3. CT SCAN- chest (assess for pleural effusion, PE, alveolar hemorrhage; monitor interstitial lung dz)
4. MRI – brain (white matter changes, vasculitis, stroke. May be absent)

**ix) Diagnosis**

a. Understanding the clinical presentation is paramount to diagnosing the condition and the clinician should be familiar w/ the diagnostic criteria (EULAR/ACR 2019) and recognize target organ damage for classification of this complex disease. If a patient has at least 2 of these symptoms, then a workup is appropriate. Biochemical testing is key and includes ANA, basic labs, and immunologic testing to confirm SLE and disprove any other possibilities (your differential possibilities). SLICC criteria (2012-

Systemic lupus International Collaborating Clinics) was released to improve upon already existing ACR 1997 classification criteria. SLICC added criteria of neurologic manifestations, relevant immune results, cutaneous manifestations, despite biopsy conformed nephritis a person could still fail ACR criteria.

i. EULAR/ACR 2019
    1. Must have +++ANA titre > 1:80 deems autoimmune is present; prefer >320 (highly suggestive SLE)
    2. Must have (1) clinical criteria and at least 10 points total
    3. Clinical criteria may have been in the past and not currently active (gathered in the HPI/ROS taking); the clinical criteria should not have another viable reason (your differential makes more sense than SLE). IN each domain, count the highest points only if you have more than one clinical feature within that criterion.
    4. Example: hematologic criterion include Leukopenia <4000/uL (3 points), thrombocytopenia (<100,00/mm3 (4 points), autoimmune hemolysis or hemolytic anemia (4 points).....INTERP: use the 4 points not the 3 points if you had all of them present. Only count the highest weighted criterion from each domain.
    5. See above in S/Sx -points will be listed in parentheses.

ii. DX criteria Sense/Spec (sensitivity & specificity)
    1. SLICC validated sense 97%/spec84%
    2. 1997 ACR validated sense 83%/spec96%
    3. EULAR/ACR 2019 validated sense 96%/spec93% **** use this one

**x) Differential Diagnosis (DDX)**

a. Method: common but drug-induced lupus (procainamide, isoniazid, and hydralazine most common, but include many others-see below). Lupus s/sx may coincide with other diseases, therefore ruling out other potential causes is paramount to making an astute diagnosis of SLE.
    i. Top10 DDX: Chronic Fatigue syndrome (r/o all other causes, diagnosis of exclusion); Behcet Syndrome (oral ulcers?, labs); dermatomyositis (r/o via rash specifics-Gottron's sign and muscle weakness); endocarditis (r/o ECG and CP); Fibromyalgia (r/o pain and clinical dx); HIV (r/o testing); hypothyroidism (r/o testing); IBD (r/u imaging and testing); Lyme disease (r/o serology and testing and HPI)
    ii. Other DDX include Acute Pericarditis (CP presenting), antiphospholipid syndrome (thrombocytopenia presenting), autoimmune hepatobiliary disease, B-Cell Lymphoma (lymphadenopathy, cell dyscrasias presenting), FM (myalgias and arthralgias presenting).

**xi) Treatment Plan**

i. Depends on severity, presenting s/sx.

1. Severity >> use tools to determine and based on EBP determine therapy
    a. Milder dz: musculoskeletal, cutaneous, and serositis manifestations
        i. choose between NSAIDS, low-potency immunosuppression (beyond hydroxychloroquine), short courses of corticosteroids.
        ii. Symptoms may wax and wane
    b. Severe dz: kidney and CNS involvement
        i. More aggressive immunosuppression & more prolonged corticosteroid use needed

ii. Assess response & remission
1. Tools used for standardized assessment
2. Eval from disease activity standpoint and patient complaints
    a. QOL (quality of life), fatigue reduction, pain reduction
    b. Quantifiable symptom reduction (choose & use a tool)
        i. SLEDAI (SLE Disease Activity Index) -clinical and laboratory variables in a weighted score
        ii. SLEDAI-2K (SLE Disease Activity Index) -clinical and laboratory variables in a weighted score >> adds persistent and active alopecia, ulcers, rash, and proteinuria.
        iii. SLE-DAS (SLE Disease Activity Score)-uses 17 symptoms and labs and has a higher sensitivity compared to the SLEDAI.
        iv. SLE-RSI (Responder Index) Ises Safety of Estrogens in SLE-national assessment, British Isles Lupus assessment group, and Physician global assessment.

iii. GOT: EULAR (European League Against Rheumatism)
1. ****Remission- no clinical activity, no use of medications (immunosuppressants or glucocorticoids)
2. Partial renal remission- greater than 50% reduction in proteinuria to sub nephrotic levels and serum creatinine within 10% from baseline
3. Complete renal remission- proteinuria <500 mg per 24 hours and serum creatinine within 10% from baseline
4. **Low disease activity- SLEDAI score <3 on anti-malarial Rx OR SLEDAI <4 on glucocorticoids dose 7.5 mg or less and well-tolerated immunosuppressants

**xii) Medications**

a. Method: Aim is remission (complete) and if not achievable, then aim for low disease activity in all affected systems. ALL SLE patients should be on hydroxychloroquine***, glucocorticoids (see specifics below), and subsequent start of immunosuppressants to prevent disease flares and to reduce steroid dosing with

aim less than 7.5 mg prednisone equivalent or DC them all together. First, determine severity

b. Know before you go: there are certain medical history concerns and this needs to be completed prior to prescribing the biologic agent >>> allergy to rubber or latex; are you taking any other immunosuppressant medications; are you prone to frequent infections; any history of hepatitis B, uncontrolled diabetes, HIV, TB, CHF, skin issues, other autoimmune diseases; and have you ever been exposed to chicken pox, measles, mumps, or rubella.
    i. Hydroxychloroquine (HCQ) – Plaquenil. A well tolerated anti-malaria agent with immunomodulator effects that reduces overall dz flares (20-40%), reduces accrued damage, and is a cornerstone in management. It also reduces kidney progression. Tolerable ADR panel.
        1. MOA- unsure of all activity made by drug but can pass through cell membrane into the lysosomes where it disrupts key cellular activity (inhibits TLR of the cGAS-STING pathway which limits enzyme and cytokine release, receptor recycling, antigen presenting, T cell polarization, and NK activation. It also increases protection against UVA and UVB light).
        2. Monitor vision mainly; educate the patient on using an AMSLER grid every 2 weeks. Report any vision changes immediately to the clinic.
        3. SPEC-POPS
            a. Crosses placenta and is equal concentration between mother/fetus
            b. Able to be used in pregnancy and breastfeeding
            c. Reduces neonatal lupus or heart block (from circulating SS-A/B antibodies)
        4. ADRs: common reactions include abdominal pain, diarrhea, N/V, and vision changes. Serious reactions include myelosuppression with agranulocytosis and hemolytic anemia in those G6PD deficient. Angioedema, bronchospasm, Stevens Johnson syndrome, exfoliative dermatitis, and (TEN) toxic epidermal necrolysis.
    ii. NSAIDS
        1. Pain, arthralgias, mild serositis, HA, and fever symptomatic relief
        2. Non-steroidal anti-inflammatory agent.
        3. May cause elevated LFTs and creatinine.
        4. Caution w/ concomitant steroids (inc. GIB and PUD)
    iii. Glucocorticoids
        1. Goal: potent anti-inflammatory but minimize use as much as possible, adding immunosuppressants should reduce steroid dosing with a goal (not in acute flare) of <7.5 mg per day.
        2. Steroids provide rapid s/sx relief. Tolerable ADR panel.
        3. Methylprednisolone, prednisone,
        4. MOA: decreases inflammation by suppressing migration of PMN (polymorphonuclear leukocytes) and reverses cap perm.

iv. Immunosuppressants
    1. DMARDS (disease modifying anti-rheumatic drugs)
        a. MOA-immune suppressants, cytotoxic (cell-killing) and anti-inflammatory effects.
            i. Toxicity -cyclophosphamide 2nd and 3rd line due to ADRs
    2. Methotrexate
        a. Use w/ poor s/sx control in patients already on steroids and HCQ or when using HCQ alone. Tolerable ADR panel.
        b. MOA- blocks purine synthesis and AICAR which increases anti-inflammatory adenosine at the sites of inflammation. Reduced inflammation well**
        c. Monitor CBC w/diff for blood issues, esp. thrombocytopenia; LFTs for elevated transaminases; folic acid level; and kidney fxn.
        d. Monitor preg. In those appropriate, take extra precautions as MTX is teratogenic and a female should not become pregnant while taking.
        e. Supplement with folic acid 1-5mg daily while on MTX; avoid sunlight; avoid EtOH.
    3. Azathioprine
        a. Use w/ poor s/sx control in patients already on steroids and HCQ or when using HCQ alone. Maintenance therapy. Tolerable ADR panel.
        b. MOA- may reduce immune cell proliferation and leads to lower autoimmune activity, it antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins.
    4. Mycophenolate mofetil (MMF)-
        a. Potent immunosuppressant for kidney involvement and SLE w/o Neuropsyche s/sx; Teratogenic and $$$$; Do not use in Neuropsyche issues. Maintenance therapy. Tolerable ADR panel.
        b. MOA-inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses purine synthesis and inhibits their proliferation.
    5. Cyclophosphamide
        a. Consider when advanced dz or organ dysfxn is present (specifically renal, heart and neuropsyche). Tolerable ADR panel.
        b. For rescue in patients with milder dz (no organ involvement) refractory to other treatments
        c. Gonadotropic effects caution in male/female of fertile
        d. MOA- act on DNA and may involve cross-linking, which may interfere with growth of normal and neoplastic cells

v. Biologic agents
    1. Belimumab
        a. Consider when extrarenal dz is present not controlled by prior RX. Tolerable ADR panel.
        b. MOA: inhibits biologic activity of monoclonal antibody (B-lymphocyte stimulator) found to reduce dz activity when combined with SOC DOC (standard of care drug of choice)
    2. Rituximab (off-label)
        a. Consider when severe dz is present and patient is refractory to first line therapies, renal, extrarenal, neuropsyche and hematologic. Tolerable ADR panel.
        b. MOA- B-cell depletion
    3. Calcineurin inhibitors
        a. Tacrolimus and Voclosporin
            i. MOA: Inhibit the action of calcineurin (activated T-cells)
        b. Tacro needs levels, goal 6-8.

vi. Adjunctive therapies
    1. Vitamin D supplementation
    2. Diet-based on patient presenting s/sx. For example, if patient presents with high lipids should be eating low fat diet
    3. Stress reduction (stress may cause a flare, so reduction is paramount in reducing possible flares)
    4. ACEi or ARB for any patient w/ proteinuria >0.5grams/24 hour or equivalent spot urine results
    5. Statin required in those w LDL greater than 100mg.dL to reduce accelerated atherosclerosis.
    6. If concomitant antiphospholipid syndrome is present recommend low dose daily ASA (aspirin) for anti-platelet activity
    7. Educated and inform about reducing known trigger exposure, avoiding UV light and other environmental escalatory factors.

c. Specific medication regimens based on systems involved
    i. Cutaneous (skin) disease
        1. Topical steroids or calcineurin
        2. Anti-malarial (hydroxychloroquine)
        3. Systemic steroids if severe
    ii. Renal (lupus nephritis)
        1. Initial phase then maintenance phase
        2. MMF, low dose cyclophosphamide DOC (drugs of choice)
        3. MMF, high dose cyclophosphamide DOC if severe presentation
        4. Risk for progression to ESRD (end stage renal disease)

5. Maintenance dose MMF or azathioprine DOC, can consider rituximab if refractory dz. Calcineurin inhibitors may be considered 2nd line agents.

iii. Hematologic
1. Thrombocytopenia <30,000/mm3
a. High dose steroids
b. Immunosuppressants w/ least BM myelotoxicity w/ consideration of IVIG for the acute phase.

iv. Neuro/psyche
1. Anti-malarial (hydroxychloroquine)
2. Systemic steroids
3. Immunosuppressants
4. If antiphospholipid antibodies are present >> add anticoagulant or antithrombotic

**xiii) Follow up and checklist**

i. _____Medication follow-up >> based on medications chosen, phone call or return visit to assess if patient is tolerating well without ADRs. Timing should be based on MOA and onset/duration of the medication.

ii. _____Quarterly visits are recommended and include laboratory testing and UA to monitor for new signs or symptoms and ADRs to therapies.

iii. _____Consultation follow-up >> based on specialists referred, evaluate if completed. Are the orders placed and do they have contact with those clinics?
1. Based on s/sx may need to refer >> infectious dz, neurologist, pulmonologist, cardiologist, gastroenterologist, nephrologist, dermatologist, or hematologist. If child-bearing age, high-risk obstetrician.

iv. _____Symptom checker >> has there been a reduction in s/sx? Passive or active follow up via telephone or RTC visit.

**xiv) Prognosis/Complications**

a. Highly variable disease pattern
i. From benign to rapidly progressive disease
1. Major complications are ESRD, heart, and stroke

ii. Prognostic factors (EULAR)
1. Clinical findings, diagnostic findings, immunologic results have certain indications if present (https://emedicine.medscape.com/article/332244-overview#a6 )
2. Clinical findings: neurologic, kidney, Skin lesions, arthritis, serositis,
3. Diagnostic study results: Anemia, thrombocytopenia, leukopenia, increased serum creatinine (sCreat) levels

iii. Immunologic test results: Serum C3 and C4 concentration (which may be low), anti–double-stranded DNA (anti-dsDNA), anti-Ro/ Sjögren syndrome A

(SSA), anti-La/Sjögren syndrome B (SSB), antiphospholipid (aPL), and anti-ribonucleoprotein (anti-RNP)

b. Survival rates
    i. Reduced life expectancy 5yr./>90%; 10yr./ >90%; 15yr./ 80%
        1. Higher in those with mucocutaneous and MS issues
        2. Lower in those with kidney and CNS disease
        3. Mortality now R/T cardiovascular events or ADRs from immunosuppressive medications such a fatal infection from neutropenia.
        4. DM, HTN, HLD, bone issues, infections, and malignant comorbidities all increase mortality.
    ii. Distinguish between disease activity and organ damage index
        1. Validated measure tools
            a. Systemic Lupus Activity Measure (SLAM)
            b. SLEDAI
            c. Lupus Activity Index (LAI)
            d. European Consensus Lupus Activity Measurement (ECLAM)
            e. British Isles Lupus Activity Group (BILAG) Index

**xv) Patient Education and Anticipatory Guidance**

a. Educate and inform on each medication, its' adherence, and ADRs; inform patient how to report/when to report r/t ADRs.
b. Emphasize the importance of routine follow-up appointments for detection and control of SLE disease. Educate why and when to present to the clinic related to any new symptoms, including fever.
c. Information, guidance, education, and prevention of heightened risks for infection.
d. Information, guidance, education, and prevention of cardiovascular disease, HLD, BP goals for risk reduction of common comorbidities and complications.
e. Information, guidance, and education of steroid based complications including osteoporosis & accelerated heart disease (atherosclerosis).
f. Educate on avoiding exposure to sunlight and UV light.
g. Encourage vaccination, educate on non-live vaccines when disease state is stable.
h. Offer and educate on smoking cessation (every visit if they smoke)
i. For patients of childbearing potential, carefully plan pregnancies (inquire every visit for that population of childbearing ages). Do not use estrogen-based products ) dz flares)

**xvi) Lupus in children**

a. Will present with a different constellations of symptoms
    i. Rash (malar), ulcers, mucocutaneous involvement, kidney involvement, seizures, fevers, lymphadenopathy, thrombocytopenia, and hemolytic anemia.
    ii. Avoid/prevent/monitor for long term complications of the dz/medications including atherosclerosis and osteoporosis.

**NEXT STEPS >>> These are all "classic presentations" of the expected diagnosis (SLE) with a few confounders (FOR YOUR DDX). It should be an "easy" diagnosis and pharmacotherapeutic (prescription) plan by someone taking advanced pathophysiology and pharmacology. If you have issues, meet with the professor, and have a 1:1 session to work through one of these together, otherwise review the answers and rationales together for synthesis of the knowledge.**

**Happy learning, Prof JaimaLee.** 😊

**Resources**

1. Various sources are paraphrased and combined to provide the most up to date information.
    a. Arcangelo. (2020). Pharmacotherapeutics for Advanced Practice – 4th ed.
    b. Dipiro, T., & Talbert, R. (2019). Pharmacotherapy-A pathophysiological Approach 10th ed.
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    g. Woo, T., & Wynne, A. (2021). Pharmacotherapeutics for Nurse practitioner Prescribers - 5th ed.
    h. https://reference.medscape.com/calculator/274/slicc-sle-criteria

i. https://acrjournals.onlinelibrary.wiley.com/doi/full/10.1002/art.41191
j. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5684575/
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l. https://www.drugs.com/hydroxychloroquine.html
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