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# An Overview of Lupus: A few practical points

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No relevant disclosures

# Learning Objectives

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**Participants will have medical knowledge to discuss:**

- **Judicious use of serology in the diagnosis and monitoring of SLE**
- **Rationale for Antimalarials in SLE**
- **Immunization for SLE patients**
- **Contraception and Pregnancy Issues in SLE**
- **Cardiovascular comorbidity in SLE**

# Overview:

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Prevalence: ~1/1000 adults

Gender
- females 80-90% (10 female:1 male)

All ages
- highest incidence 15-44 years
- highest prevalence 45-64 years

Ethnicity
- more common and severe in Hispanics, African Americans, Asians, North American Indigenous

# Systemic Lupus Erythematosus:
## *The challenge for treatment and research*

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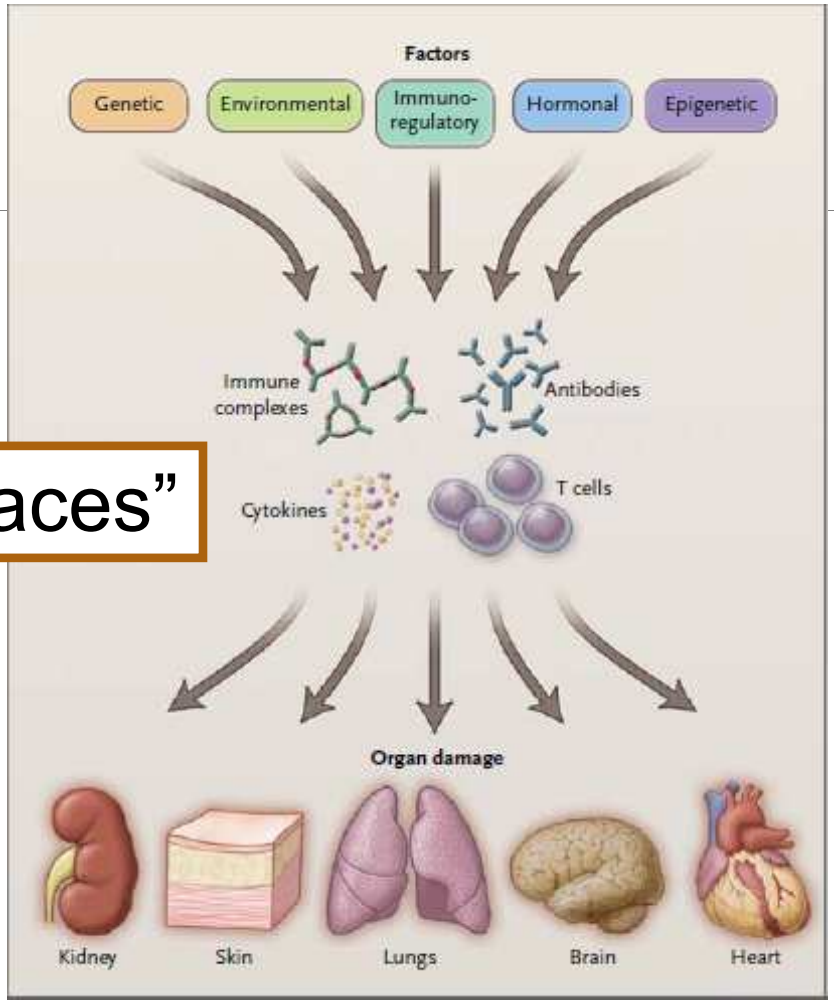
- **Very heterogeneous disease**
- **Looks different in different people**
- **No definitive diagnostic test**
- **No good tests for disease activity**
- **No good tests to predict outcome**

# Overview:

"Disease of 1000 Faces"

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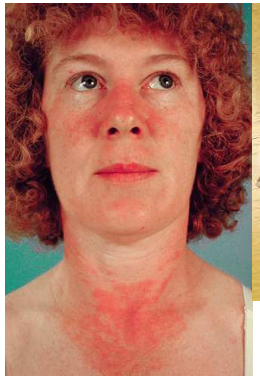
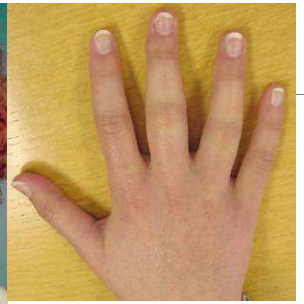
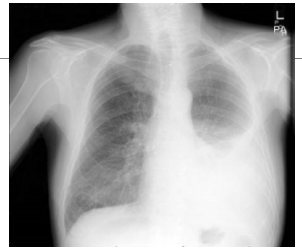
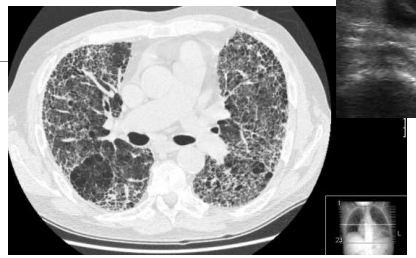
35 year old female with arthritis, rash, fatigue

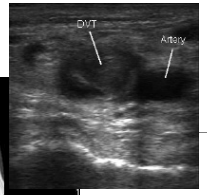




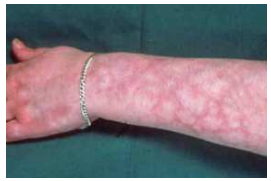
44 year old male with pleuritis, interstitial lung disease, DVT

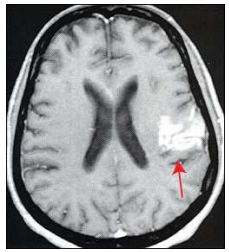




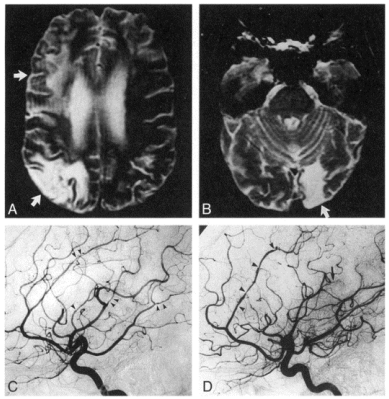


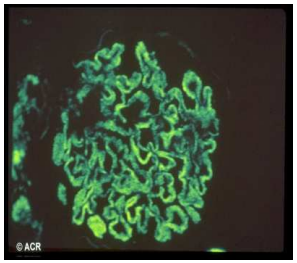

31 year old female with a stroke, rash, pregnancy losses





13 year old female with seizures glomerulo-nephritis




# SLE: Variable Presentation

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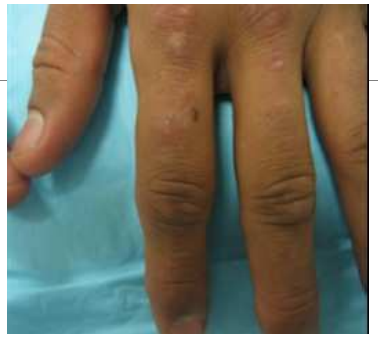
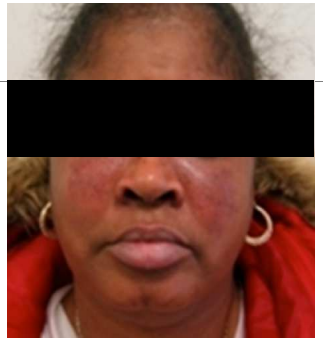
# Lupus on the Outside

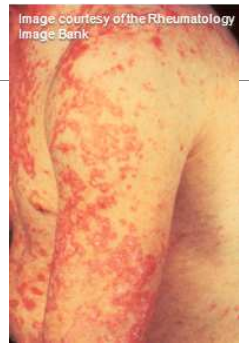


Synovitis



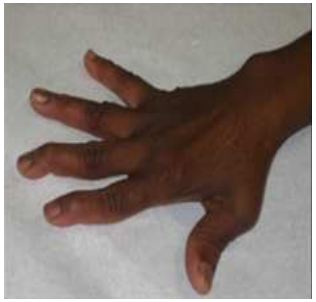
Malar rash


Oral ulcer

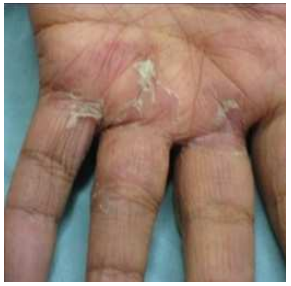



Subacute cutaneous lupus erythematosus

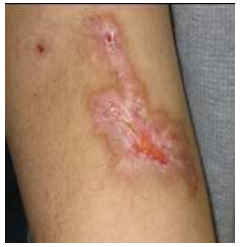
Discoid rash



Jaccoud's arthropathy

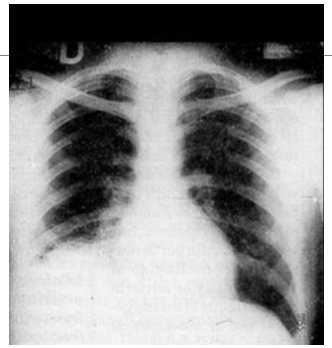


Vasculitis



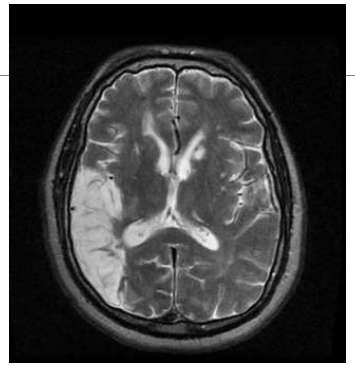
Lupus profundus

# Lupus on the Inside

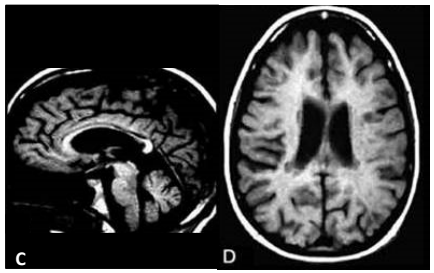


Serositis

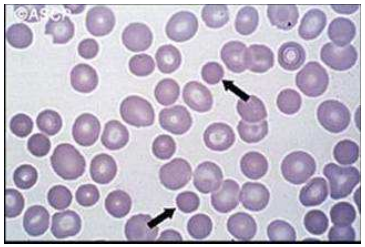

Pericardial effusion



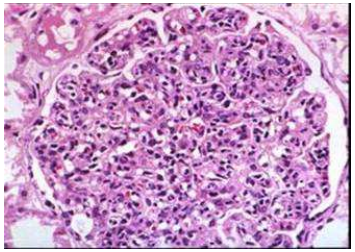
Cerebral infarct




Brain atrophy



Spherocytes

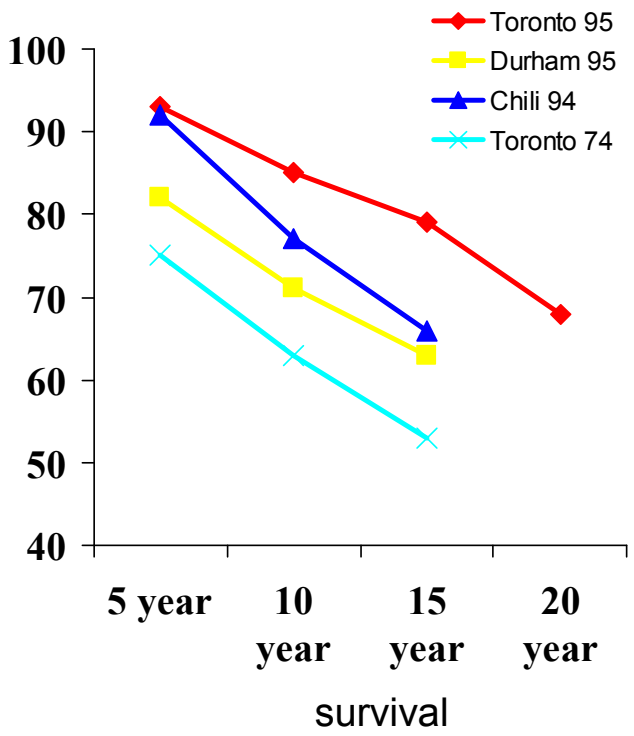


Glomerulonephritis

# SLE trends in mortality

Survival rates improving with better therapies

Mortality still 3X higher than general population



# Systemic Lupus Erythematosus. Definition:

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**Systemic autoimmune disease**

- **Chronic, multi-system, inflammatory**
- **Diverse array of clinical manifestations**
- **Severity ranges from mild to rapidly fatal**
- **Characterized by the production of autoantibodies to the cell nucleus**

# Judicious use of serology in the diagnosis and monitoring of SLE

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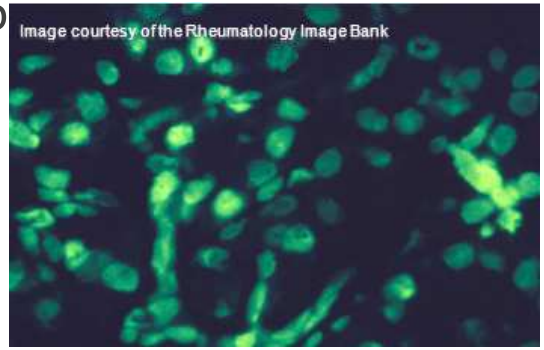
**What Do All Lupus Patients Have in Common?**

—**<u>Antinuclear Antibodies (ANA)</u>.**

- **Multiple methods for detection but immunofluorescence (IF) is the most reliable**
- The ANA test is highly sensitive for SLE but specificity is poo
- A positive ANA test result can occur in many other disease states as well as in a large number of healthy individuals.




ANA present in 95%–98% of SLE patients

# Judicious use of serology

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## ANA testing:

**ST. BONIFACE HOSPITAL TESTS**

**Systemic Autoimmune Disease**

- ☐ ANA SCREEN ..... ANA
- ☐ dsDNA ..... DNA
- ☐ ENA (includes the following group of 6 antigens)
  - ☐ SSA (Ro) ..... SSA
  - ☐ JO-1 ..... JO1
  - ☐ Sm ..... SM
  - ☐ SSB (La) ..... SSB
  - ☐ Scl-70 ..... SCL
  - ☐ Sm/RNP ..... RNP
- ☐ Centromere B ..... CENB
- ☐ Hep2 ..... HEP2

**Rheumatoid Arthritis**

- ☐ Cyclic Citrullinated Peptide ..... CCP

**Celiac Disease**

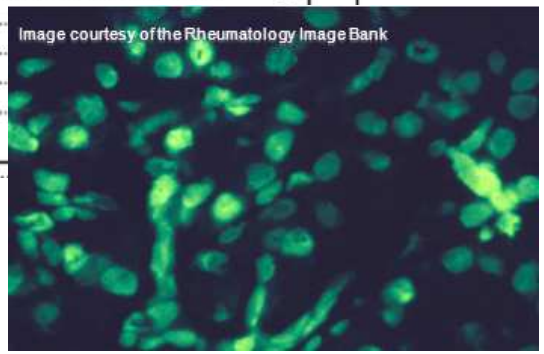
**HEALTH SCIENCES CENTRE TESTS**

**Protein Quantitation (Serum)**

- ☐ IgG ..... IGG
- ☐ IgA ..... IGA
- ☐ IgM ..... IGM
- ☐ IgG Subclasses ..... IGGS
- ☐ Complement C3 ..... C3
- ☐ Complement C4 .....
- ☐ Rheumatoid Factor (RF) .....
- ☐ Free Light Chain Ratio .....
- ☐ C1 Esterase Inhibitor .....

ANA by ELISA present in 65-75% of SLE patients at diagnosis

ANA by IF present in 95%–98% of SLE patients at diagnosis



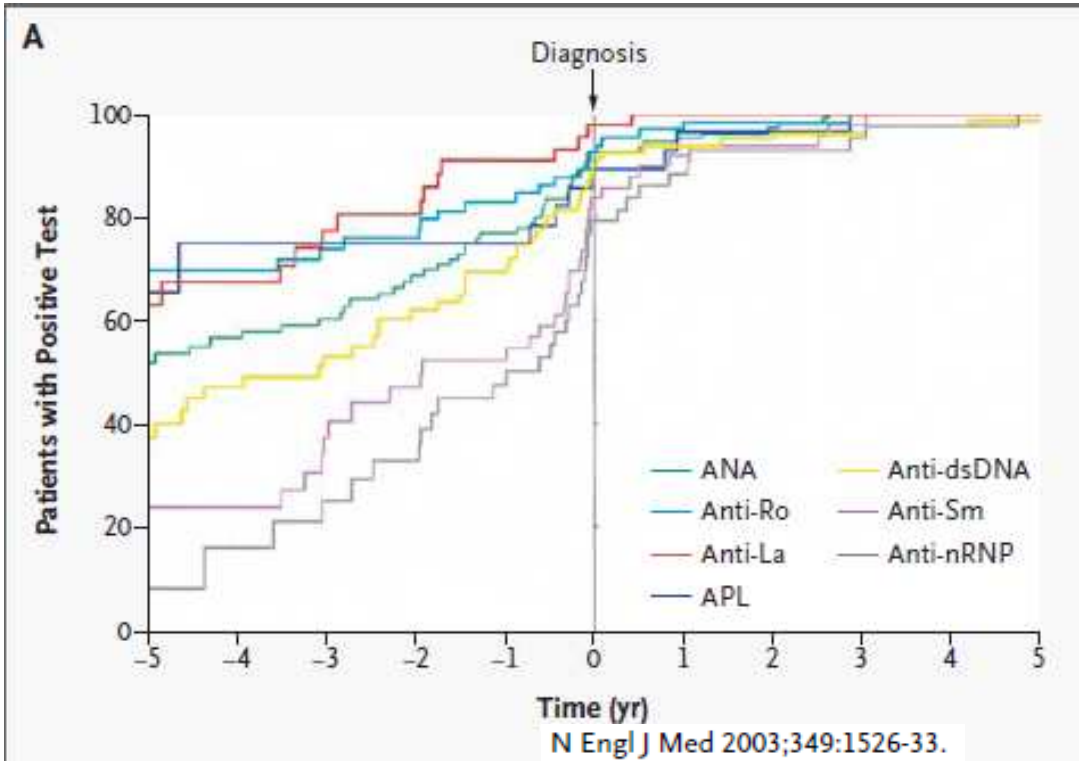

ANA present in 95%–98% of SLE patients

# Judicious use of serology

**Autoantibodies *PRECEDE* the diagnosis**

- **A negative IF ANA makes a diagnosis of lupus <u>very</u> unlikely**

Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus




N Engl J Med 2003;349:1526-33.

# Judicious use of serology

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**Lady Gaga Says She's "Borderline Positive for Lupus"**

**What does that mean?**

**Lupus is a clinical diagnosis!!**

**There are NO laboratory tests to determine if one has lupus or not. The ANA test is *NOT* a screening test**

**A positive ANA does not make the diagnosis**

**A negative ANA does not completely rule out the diagnosis (But almost)**

***At least* 10-15% of healthy women have a positive ANA**

# Assessment of Disease Activity in SLE


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Antinuclear antibodies **DO NOT** fluctuate with disease activity

- ANA may become negative over time in some patients, even with ongoing disease activity

- Extractable Nuclear Antigens **DO NOT** fluctuate with disease activity

Serum titer of anti-dsDNA and serum complement are the most common and probably the most useful serologic tests for assessing disease activity, but have important limitations.

# Assessment of Disease Activity in SLE


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## dsDNA antibodies **MAY** fluctuate with disease activity

- Only ~50% of SLE patients ***ever*** have positive dsDNA antibodies
- Some patients ***always*** have very high titre dsDNA antibodies
- In a ***subset*** of patients rising dsDNA antibodies will herald a disease flare
- Rising dsDNA antibodies alone are not sufficient reason to change treatment

# Assessment of Disease Activity in SLE

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Acute exacerbations of SLE can often be associated with low serum complement (C3, C4) levels.

Serial measurements of C3 and C4 levels can be very helpful to compare to a patient's own baseline levels

*But:*

- Many SLE patients ***never*** have depressed complement levels
- Some patients ***always*** have depressed complement levels

Serum Complement Levels in Systemic Lupus Erythematosus, Dubois" Lupus Erythematousu and Related Syndromes, 8th Edition

# Assessment of Disease Activity in SLE

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***The erythrocyte sedimentation rate (ESR) is the most useful non-specific marker for distinguishing between active and inactive SLE***

*BUT:*

- ESR may be normal even in the presence of major organ involvement
- Conversely, ESR may remain raised in remission, being maintained by changes in immunoglobulins and Proteins

E Hay, C Gordon and P Emery. Assessment of lupus: where are we now? Annals of the Rheumatic Diseases 1993; 52: 169-172

# Assessment of Disease Activity in SLE

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Look for Non-specific markers of inflammation:

- Anemia of chronic disease
- Low albumin
- Increased Platelets
- Lymphopenia

Urinalysis is a should be performed routinely

- Casts
- Protein
- Cells

B. Griffiths et al. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. Best Practice & Research Clinical Rheumatology Vol. 19, No. 5, pp. 685–708, 2005

# Summary: Judicious use of serology


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ANA is not a screening test:

Do not order an ANA unless there is a high clinical suspicion for SLE

A negative IF ANA effectively rules out the diagnosis

Be aware whether your lab uses ELISA or Immunofluorescence

Immunization for SLE patients

Monitoring of disease activity is complicated and must be individualized

# Rationale for Antimalarials in SLE


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**Principles of Management: Lupus is a spectrum of diseases**

- **Individual manifestations, not the diagnosis, guide the treatment**
- **Management requires short-term AND long-term approach:**
- **Suppression of Disease Activity**
- **Prevention of Complications/Damage/ Comorbidity**
- **Damage comes from disease activity AND treatment**

# The New Role of Antimalarials In SLE

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## A PARADIGM SHIFT

**Previous recommendations for Antimalarials:**

- ***'Indication for Antimalarials limited to patients with non-major organ involvement'.***[1]

1.Klippel JH. Systemic Lupus Erythematosus: Management. In Rheumatology 2nd ed; Klippel JH, Dieppe PA Eds.; Mosby London, 1994; pp6.4-6.5.

# The New Role of Antimalarials In SLE

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## A PARADIGM SHIFT

## More Recent Literature:

***"Hydroxychloroquine: the cornerstone of lupus therapy" [2].***

***"Why all systemic lupus erythematosus patients should be given hydroxychloroquine treatment"[3]***

***"Hydroxychloroquine is 'lupus health insurance' "[4]***

2.Ruiz-Irastorza G, Khamashta MA; *Lupus* 2008, **17**(4):271-273. 3.Costedoat-Chalumeau N, Leroux G, Piette JC, Amoura Z: *Joint Bone Spine* 2010, **77**(1):4-5. 4. Petri M: **Lupus in Baltimore: evidence-based 'clinical pearls' from the Hopkins Lupus Cohort**. *Lupus* 2005, **14**(12):970-973.

# The New Role of Antimalarials In SLE

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## A PARADIGM SHIFT

- **Recommend treatment with antimalarials, preferably Hydroxychloroquine, for *all* patients with SLE."**
  - Starting as soon as diagnosis made.
  - Maintained long term if toxicity does not ensue, whatever the subsequent course of lupus (pregnancy included) and the additional medications needed.

1.Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA: **Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review.** *Ann Rheum Dis* 2010, 69(1):20-28.

# Rationale for Antimalarials in SLE

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**Benefits of Antimalarials:**

- **Multiple studies clearly showing reduced disease activity with use of antimalarials**
- **Multiple studies clearly showing improved Nephritis Outcomes**
  - Reduced incidence & prevalence of renal involvement
  - Increased sustained remissions
  - Prolonged time to end-stage renal failure
- **Decreased skin and joint flares**
- **Decreased risk of major organ flare: 6 fold reduction in severe flares, 57% reduction in major flares (nephritis and vasculitis).**

# Rationale for Antimalarials in SLE


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**Benefits of Antimalarials:**

- 38-50% mortality reduction
- Hydroxychloroquine use associated with improved lipid profile:
  - **↓ triglycerides, ↓ LDL cholesterol and/or VLDL cholesterol , ↑ HDL cholesterol, ↓ apolipoprotein B**
- Possible protective effect for atherosclerosis
  - Lower prevalence of carotid artery plaques
  - Decreased arterial stiffness

# Rationale for Antimalarials in SLE

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**Benefits of Antimalarials:**

- Improved Glucose metabolism
  - improved glucose profiles
  - lower fasting insulin levels
  - lower insulin resistance
  - lower HbA1c
  - Possible reduced frequency of metabolic syndrome

Mechanism:

- improves binding of insulin to its receptor, thereby improving glucose tolerance

# Rationale for Antimalarials in SLE


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**Benefits of Antimalarials:**

- Reduction in thrombotic effects:
- **Consistent effect of Antimalarials in preventing thrombotic events**
  - **Both venous and arterial**

- **Overall evidence for high magnitude effect**
  - **Possible dose effect**

# Rationale for Antimalarials in SLE

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**Benefits of Antimalarials:**

- Improved Pregnancy Outcomes
  - **Reduced maternal disease activity**
  - **Reduced incidence of neonatal lupus**

# Rationale for Antimalarials in SLE

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**Increased risk of retinopathy!**

- Previously thought to be rare
- Associated with daily and cumulative dose- **Not so rare!**
- **Risk reaches 1% at ~5 years**
- Important but manageable toxicity

# Rationale for Antimalarials in SLE

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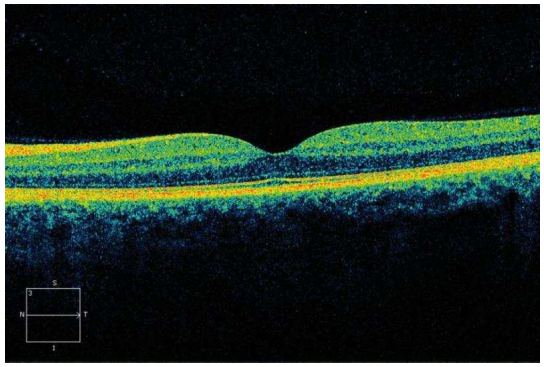
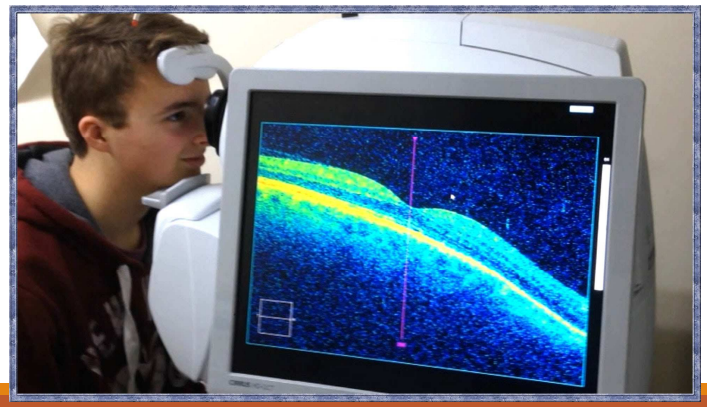
**Monitoring Guidelines for retinopathy!**

- Keep dose ≤5mg/kg
- Baseline eye exam within 1st year including OCT (optical coherence tomography)
- Annual eye exam thereafter
- Annual OCT after 5 years
- Can be done by Ophthalmology or Optometry





# Summary:
# Rationale for Antimalarials in SLE

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***Improvement in rashes and arthritis***

- ↓ ***disease activity***

***Improved nephritis outcomes***

***Flare prevention/ maintenance of remission***

***Improved lipid profile/ atherosclerosis*** ↓

***Improved Glucose metabolism***

- ↓ ***Thrombotic events***
- ↓ ***Infections***
- ↓ ***Damage Accrual/ Mortality*** ↓

***Improved Pregnancy outcomes***

**Important to monitor for Retinopathy!**

**Cost $250-$500/ year**

# Immunization for SLE patients

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**(Added) Reasons to vaccinate SLE patients:**

- Infection is a leading cause of morbidity and mortality among SLE patients.
  - Dysfunction of the innate and adaptive immune systems increases the risk of infection in patients with SLE.
  - Significant additional risk related to immunosuppressive medications
  - In some patients chronic organ damage (e.g. lung, heart, kidney) adds further to the risk.

# Immunization for SLE patients


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**Common questions about vaccines in SLE:**

- ***Will immunizations cause lupus to flare?***

  - **No.** There is no evidence for immunizations causing a clinical flare of SLE.
    - Some studies have shown upregulation of some SLE related immune pathways post vaccination, without evidence of clinical flare.

# Immunization for SLE patients

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**Common questions about vaccines in SLE:**

- ***Will immunizations be effective for SLE patients taking immunosuppressives?***

  - Immunizations may be slightly less effective in severely immunosuppressed patients.
    - These patients are at highest risk *'better than nothing'*.

# Immunization for SLE patients

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**Common questions about vaccines in SLE:**

- ***Are live vaccines safe in SLE patients?***

  - Live vaccines are **contraindicated** in patients on biologic therapies and in those on high dose immunosuppression.

# Immunization for SLE patients

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***Which vaccines are live?***

**Shingles vaccine**

**MMR**

**Flumist (Influenza Vaccine; nasal spray)**

**Oral Polio Vaccine**

**Varicella (chickenpox) Vaccine**

# Immunization for SLE patients

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**What is high dose immunosuppression?**

- Cyclophosphamide
- High dose prednisone (40-50mg/day)
- Moderate dose prednisone (>20mg) ***plus*** immunosuppressant such as azathioprine, mycophenolate, methotrexate, tacrolimus, leflunomide etc.
- *Antimalarials are NOT immunosuppressive*

# Immunization for SLE patients

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**What biologics are used in SLE?**

- Rituximab (effects last several months post infusion)
- Belimumab
- Abatacept
  - *(Lots more coming)*

# Immunization for SLE patients

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## What about Human papillomavirus vaccine for SLE patients?

- Some types of HPV are strongly related to pre-malignant cervical abnormalities and cervical cancer.
- HPV infections are more prevalent in SLE patients when compared to the healthy population.
- SLE patients have higher rates of cervical cancer.
- Therefore vaccine is strongly recommended for SLE patients

# Immunization for SLE patients

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## Additional vaccination considerations for SLE patients:

- ***Planning for the future:***
- ***Lupus disease activity fluctuates:***
  - Risk of infection is highest when disease activity and immunosuppression are highest.
  - At this same time, Immunization may be less effective/unsafe.
- Therefore consider vaccinating during low disease activity/low therapy states

# Immunization for SLE patients

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**Summary:**

- All ‘usual’ vaccines strongly recommended
- Caution with live vaccines depending on therapy
- Consider HPV vaccine
- Consider additional vaccines during low disease activity states.

# Contraception and Pregnancy Issues in SLE


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**Pregnancy outcomes in SLE:**

- **Higher risk of pregnancy loss (even without antiphospholipid antibodies)**
- **Higher risk of premature delivery**
- **Higher risk of IUGR**
- **Some risk of maternal SLE flare**

***All of the above reduced if lupus well controlled, inactive at time of pregnancy***

# Contraception and Pregnancy Issues in SLE


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**Safe Lupus Medications during Pregnancy:**

- **Prednisone**
- **Azathioprine**
- **Hydroxychloroquine**

# Pregnancy and SLE: Use and safety of Antimalarials

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- ***Maternal Lupus Disease Activity:***
  - **2 Observational Studies, >500 pregnancies [1,2]**
    - **Results**: no change in pregnancy outcome, ↓ disease activity, ↓ flare, ↓ steroid dose on HCQ,
    - **RCT of 22 pregnancies[3]: no change in pregnancy outcome, ↓ disease activity, ↓ flare, ↓ steroid dose on HCQ**
- ***Neonatal Lupus:***
  - **Small case-control study[4] :**
    - **In mothers with SLE with anti-SSA/Ro/SSB/La antibodies, HCQ during pregnancy decreases the risk of cardiac conduction defects in babies**

1. Clowse ME et al: **Hydroxychloroquine in lupus pregnancy**. *Arthritis Rheum* 2006 2. Cortes-Hernandez JM: **Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies**. *Rheumatology (Oxford)* 2002, 3. Levy RA: **Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study**. *Lupus* 2001 4. Izmirly PM, Kim MY, Llanos C, Le PU, Guerra MM, Askanase AD, Salmon JE, Buyon JP: **Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine**. *Ann Rheum Dis* 2010

# Pregnancy and SLE: Use and safety of Antimalarials

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**Systematic review of AMs in pregnant patients with SLE.[1]**

- **No association of HCQ with any increased risk of:**
  - congenital defects
  - spontaneous abortions
  - fetal death
  - pre-maturity
  - decreased numbers of live births

**Ocular toxicity in children exposed in utero to AMs[2]**

- **Current evidence suggests no fetal ocular toxicity of AMs during pregnancy**
- 12 studies with a 588 offspring
- In 3 small cohorts, 6 infants had electroretinogram abnormalities at 3-7 months, all had normal fundoscopies by 4 years

1 Sperber K, Hom C, Chao CP, Shapiro D, Ash J: **Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases**. *Pediatr Rheumatol Online J* 2009. 2. Osadchy A, Ratnapalan T, Koren G: **Ocular toxicity in children exposed in utero to antimalarial drugs: review of the literature**. J Rheumatol 2011

# Contraception Issues in SLE

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## Oral Contraception [1]

- *Individualize*
- No ↑ flares if low disease activity
- Avoid estrogen if thrombotic risk :
  - anti-phospholipid Ab/ lupus inhibitor or prior thrombotic events
- Post-menopausal HRT [1]: use non-hormonal methods

1. Lateef J Autoimmunity 38 2012

# Summary: Contraception and Pregnancy in SLE


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- **Planning pregnancy is important!**
- **Continue Antimalarials throughout pregnancy**
- **May be necessary to avoid estrogens in some patients**

# Cardiovascular comorbidity in SLE

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## The Concept of Lupus 'Damage'

***Damage*= accrual of irreversible organ damage due to *disease or treatment***

**Typical Patient with Longstanding Severe Lupus:**

**Age 45-55, Inactive lupus**

Compression fractures, Cataracts

Hypertension, Chronic Renal failure

***Premature Atherosclerosis***

# Cardiovascular comorbidity in SLE

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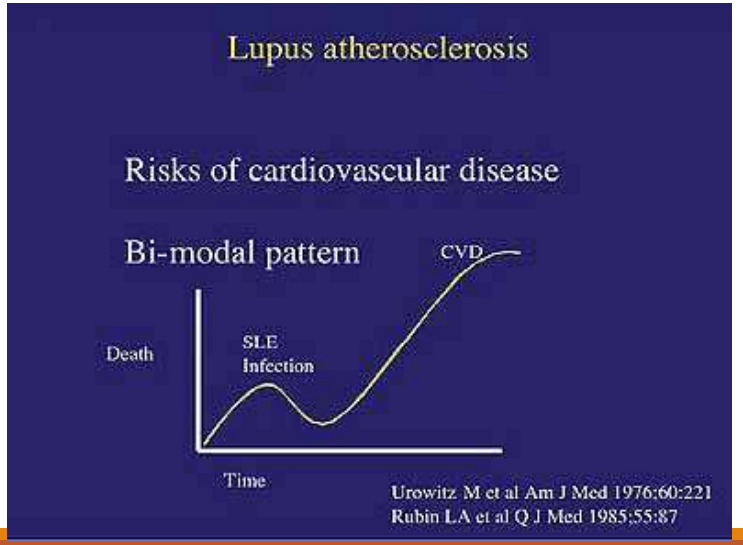
**Premature atherosclerosis is the major cause of death later in the course of SLE:**

- Attributed to chronic activation of the immune system, ***plus*** increased frequency of conventional risk factors
- 5-fold risk of MI in lupus patients
- Average age of MI ~49 yrs vs. 65-74 yrs in general population
- Leading cause of mortality in the west



# Cardiovascular comorbidity in SLE

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## Concept of Accelerated Atherosclerosis in Lupus Patients

- Women sometimes present atypically
- Vasculitis can cause MIs, but extremely rare
- Traditional risk factors are more prevalent in lupus patients but do not fully explain the increased risk
- ***Therefore:***
- A high degree of suspicion is essential to diagnose and treat, even at "young" ages
- Control modifiable risk factors (blood pressure, glucose, tobacco exposure, lipids, sedentary lifestyle), even at "young" ages

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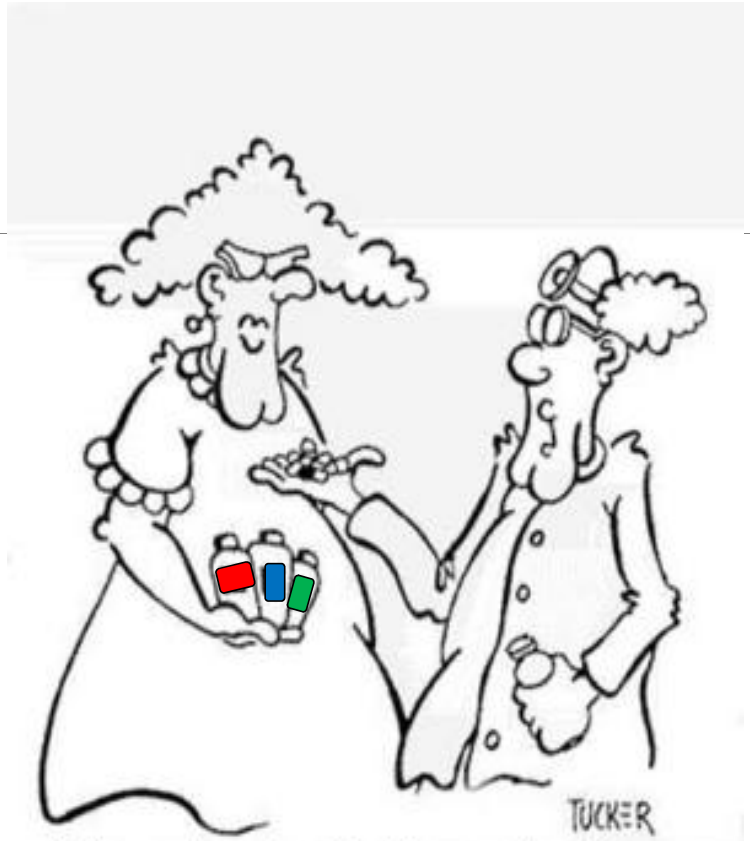
# *Damage Control in SLE*




**"The red are for your lupus, the blue are for the side effects of the red, and the green are for the side effects of the blue."**

# Summary

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- Judicious use of serology only when high clinical suspicion
- Antimalarial therapy in all patients if at all possible,
  - With attention to retinopathy monitoring
- Immunization to reduce infection
  - Caution with live vaccines
- Be aware of possible pregnancy Issues
- Aggressive management of Cardiovascular risk factors

# Thank you


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Questions?