Juvenile SLE

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Overview

- Epidemiology and aetiology
- Clinical features and classification criteria
- Assessment and monitoring of disease activity
- Management/treatment
- Prognosis
- Neonatal lupus

Epidemiology and aetiology

Juvenile onset SLE

- 15-20% of cases present in children ≤16 yrs
- Median age of diagnosis in children is 12.1 yrs
  - Rare under the age of 4 yrs
- Incidence around 10-20/100,000/yr
- jSLE F:M 5:1 (9:1 in adults)
- More common in non-Caucasians
- Polygenic, with environmental factors
- **Pathology: dysregulation humoural and cellular immunity**
  - Autoantibody production: HLA-DR association
  - B cell hyperactivity, auto-reactive T cells
  - Immune complex deposition
  - Driven by large apoptotic load through impaired clearance '**Waste disposal**' hypothesis.
- Monogenic forms exist

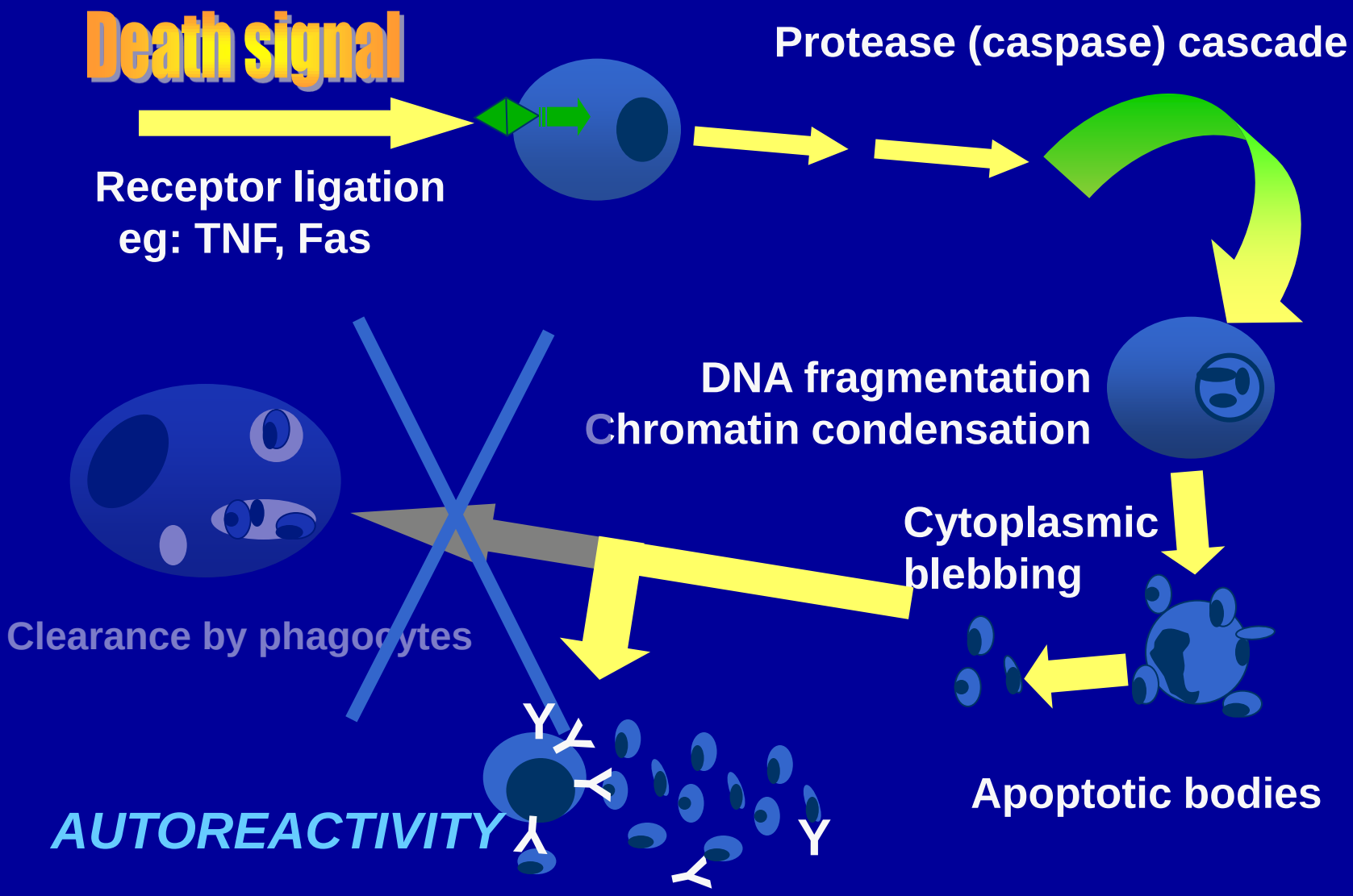
Evidence for genetic influence

- Siblings of patients with SLE have 10-20 fold increased risk of developing disease.
- Monozygous twins have 24% concordance rate versus 2% dizygotic twins.
- Familial autoimmunity is a risk factor for SLE (OR 4.1 with 1 relative, 11.3 with 2 or more relatives).
- Increased susceptibility to SLE is associated with an increasing number of recognized candidate genes, including HLA haplotypes, ITGAM, IFR5, BLK, STAT4, PTPN22, and Fcγ receptor polymorphisms.

Evidence for environment

- Ultra-violet (UV) light can induce flares, possibly by altering DNA methylation
- Viruses
- Hormones
- Drugs (e.g. hydralazine) have been shown to impair T cell DNA methylation leading to increased autoreactivity

Waste disposal hypothesis

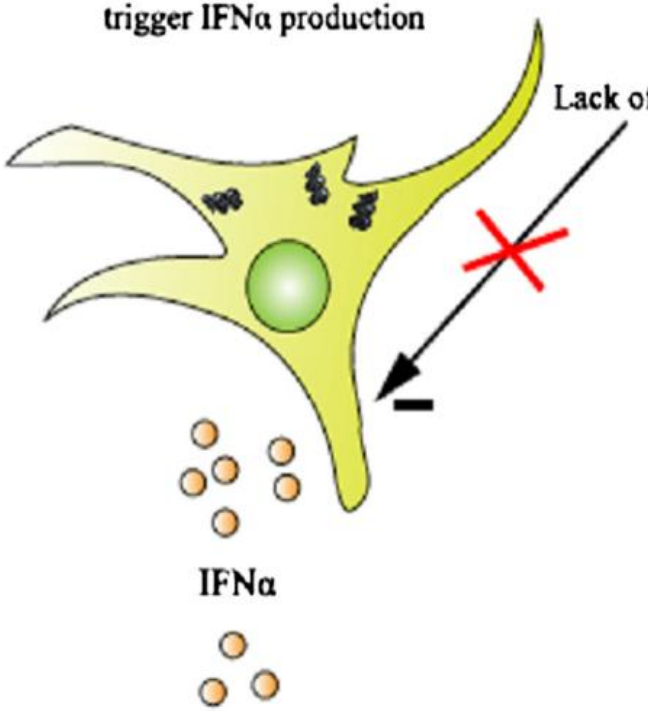


Monogenic SLE

Abnormal Cytokine signalling pathways | **immune-complex processing** | **adaptive and autoantibody production**

TREX1
RNASEH2A/B/C
SAMHD1, ADAR1

intracytoplasmic DNA accumulation
trigger IFNα production

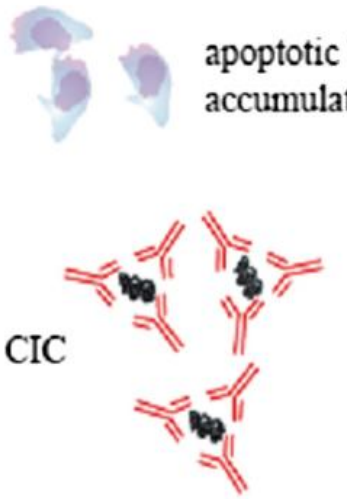


-Cytoplasmic DNA can promote IFNα production
-High level of IFNα is associated with autoimmunity

C1q/r/s, C2, C4

Complement deficiency:

Classical pathway defects induce
increase of apoptotic bodies
and circulating immune complexes (CIC)
Lack of regulatory functions of C1q on IFNα production

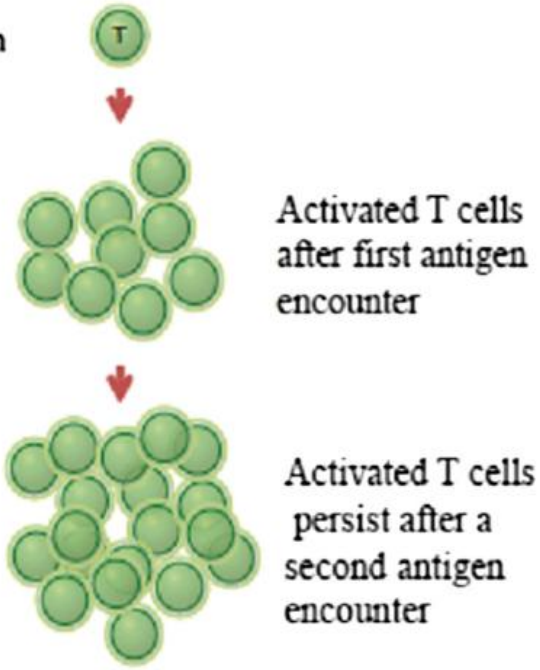


-Complement is a major regulator of
apoptotic bodies and CIC clearance
-Increased level of apoptotic bodies and CIC
is associated with SLE

Fas

FasL deficiency:

Apoptosis defects induce
activated T cells persistance



-Activation induced cell death defects
promote autoimmunity

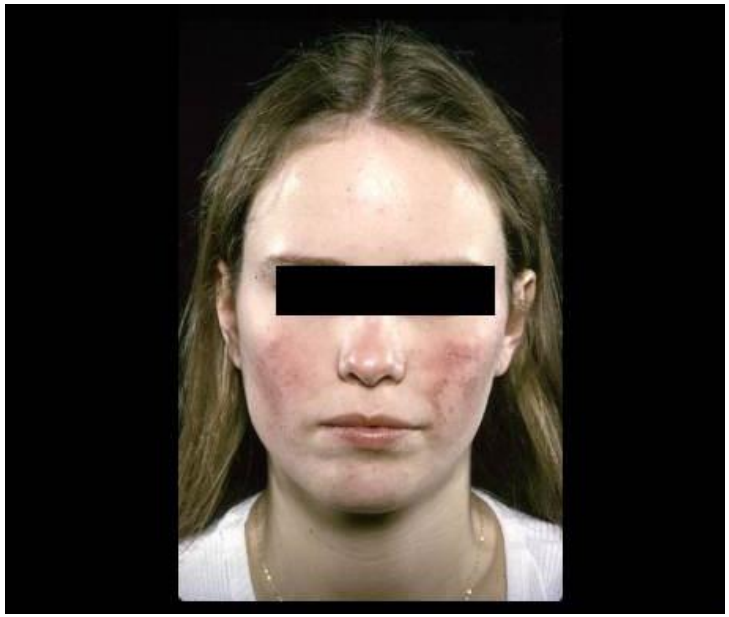
Belot and Cimaz. Pediatric Rheumatology 2012, 10:21

Clinical features and classification criteria

Updated ACR Classification criteria

(Hochberg et al, Arthritis Rheum 1997 40:1725)

Criteria (require 4/11)
Malar rash
Discoid rash
Photosensitivity
Oral or nasal ulcerations
Non erosive arthritis
Nephritis
Encephalopathy
Pleuritis or Pericarditis
Cytopenia
Positive ANA
Positive dsDNA / Sm / aCL / LA



SLICC classification criteria for SLE

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

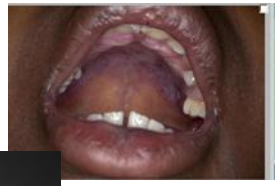
Petri M, et al. Arthritis and Rheumatism. Aug 2012

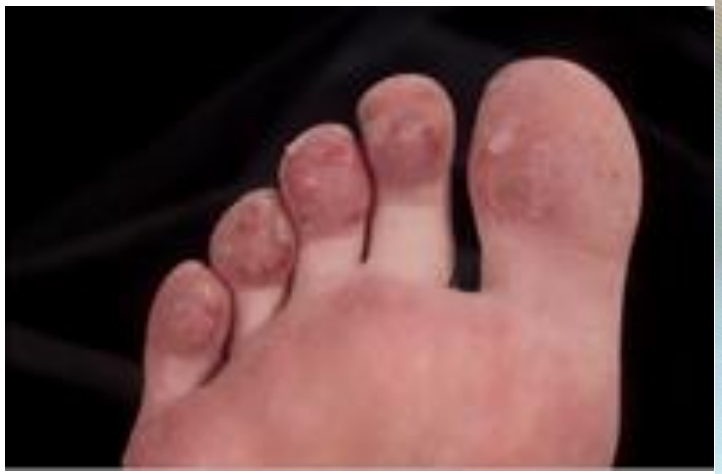
Clinical characteristics of JSLE

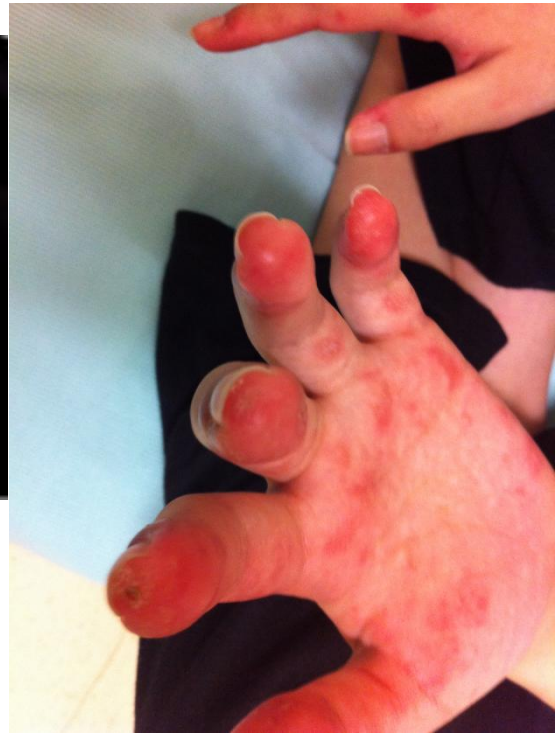
Disease manifestation	Juvenile onset SLE	Adult onset SLE
Rash	40-60%	60-80%
Photosensitivity	35-50%	35-50%
Alopecia	15-30%	20-55%
Arthritis	60-70%	**80-95%**
Renal disease	**60-80%**	35-50%
CNS disease	**20-45%**	10-25%
Pulmonary involvement	15-40%	**20-90%**
Pericarditis	10-15%	25-30%
Lymphadenopathy	20-30%	15-25%

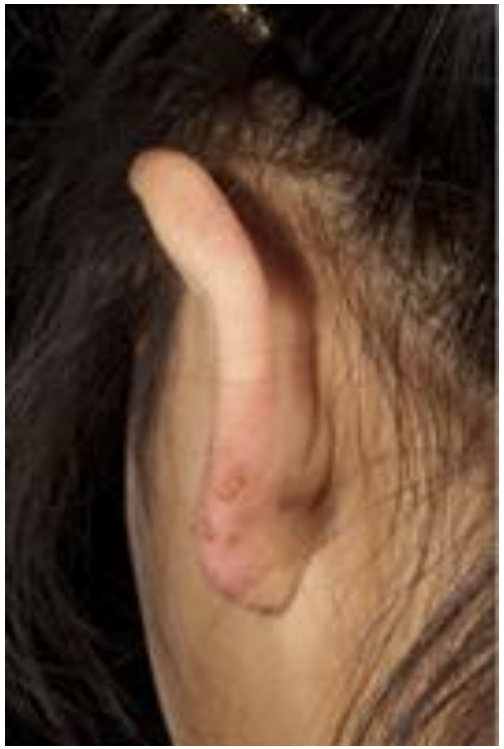
Papadimitraki and Isenberg. Exp Rev Clin Immunol 2009;5:391-403
Morgan TA et al. Lupus 2013; 22:1309-1319

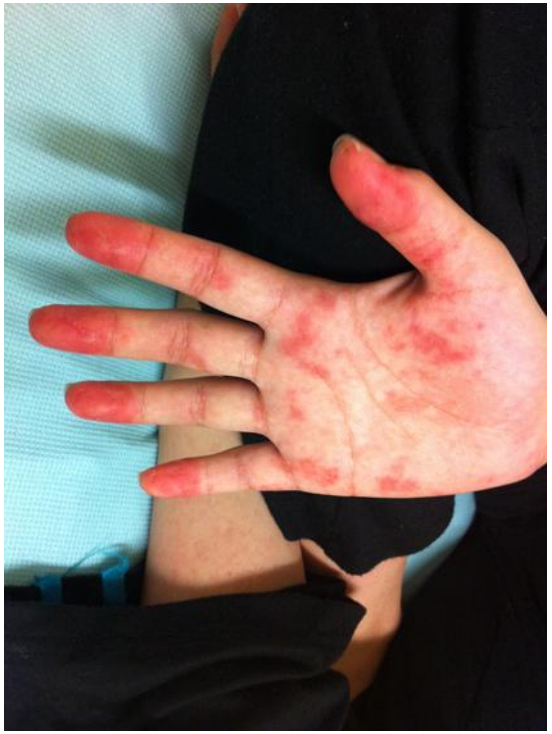
Cutaneous manifestations

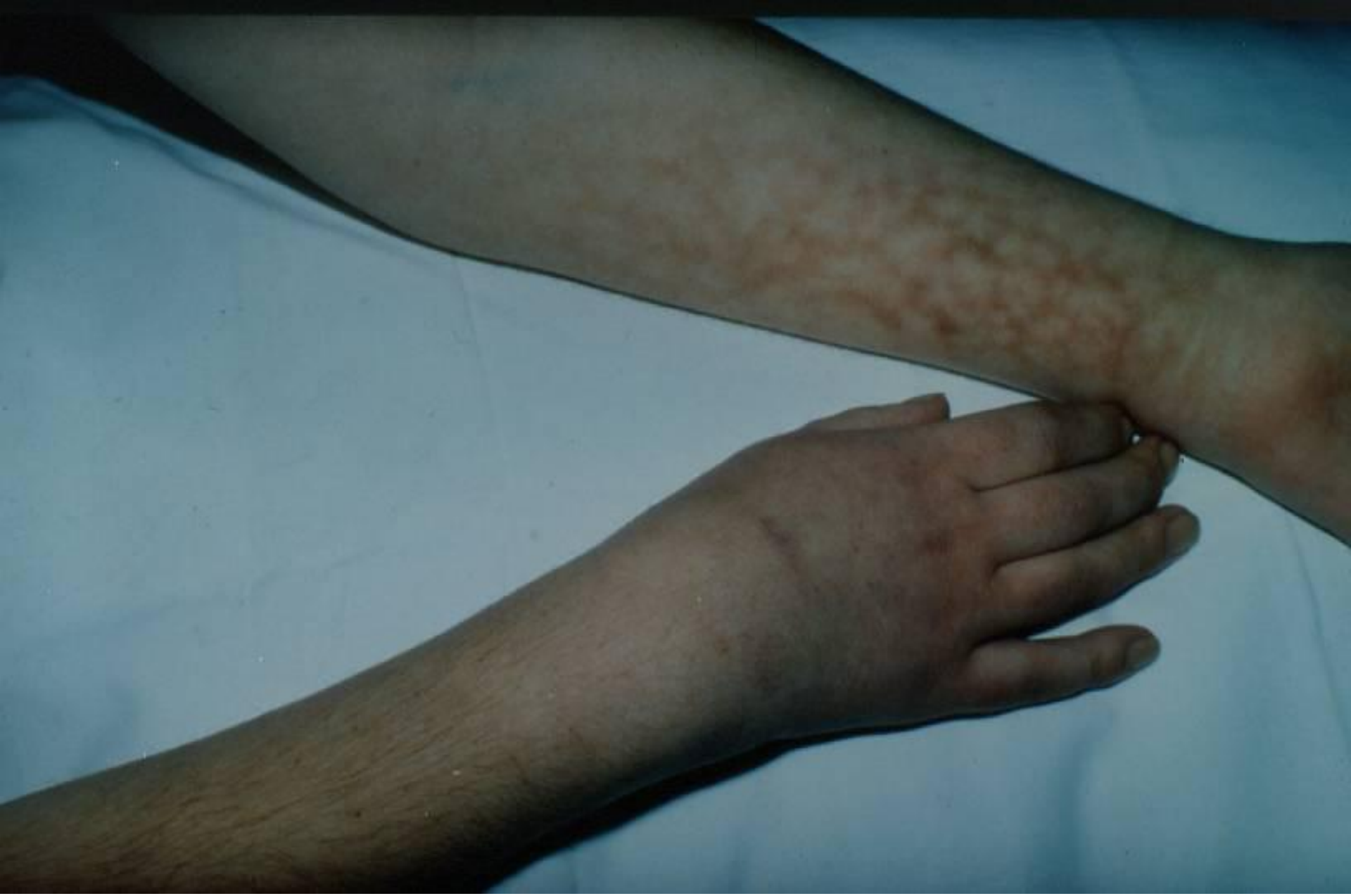


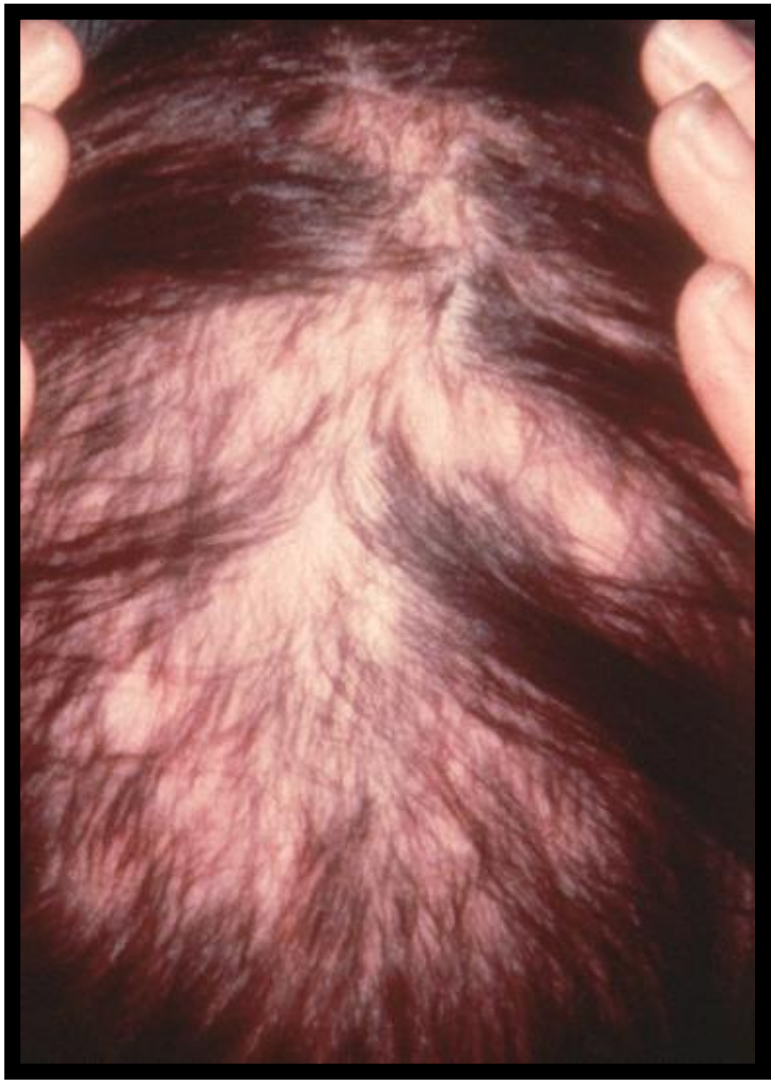












Lupus nephritis

Lupus nephritis

- present in 60 - 80% of JSLE cases
- influences management with immunosuppressive agents
  - earlier and more severe presentation in patients with JSLE (compared to adult-onset) SLE
- Presentation of renal involvement
  - proteinuria
  - microscopic (and rarely macroscopic) haematuria
  - nephrotic syndrome
  - hypertension
  - evidence of renal dysfunction
    - elevated plasma creatinine or reduced estimated glomerular filtration rate

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis

Class I	**Minimal mesangial lupus nephritis** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity or mesangial matrix expansion
Class III	**Focal proliferative lupus nephritis** Active or chronic focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli

International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification of Lupus Nephritis

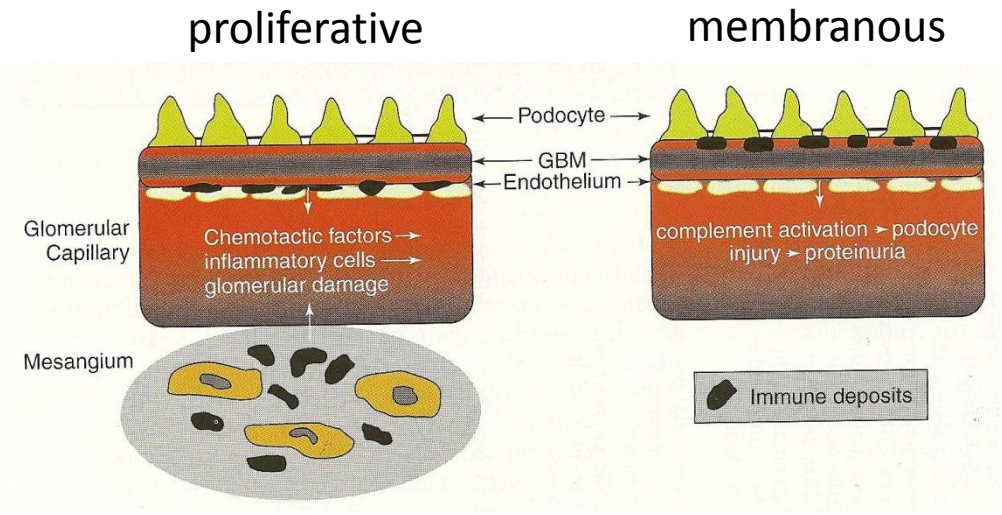
Class IV **Diffuse proliferative lupus nephritis**

Active or chronic diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥ 50% of all glomeruli.

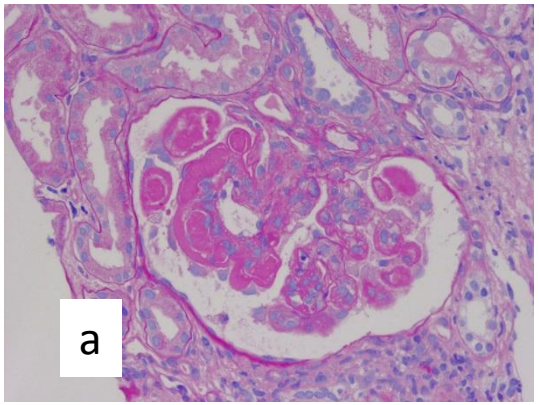
International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
Class VI	**Advanced sclerosis lupus nephritis** >90% of glomeruli globally sclerosed without residual activity

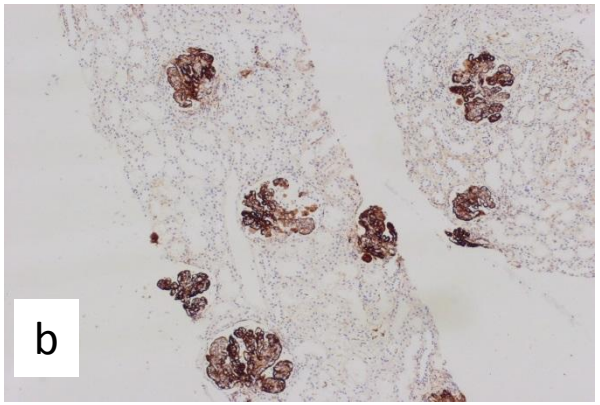
Lupus nephritis



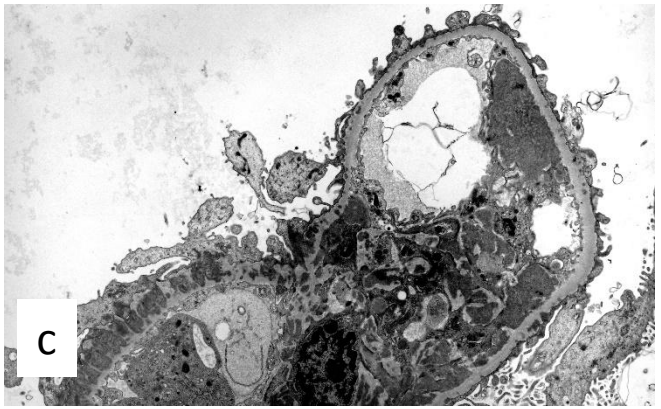
Class 4: diffuse proliferative



Massive subendothelial deposits:
"Wire loop"

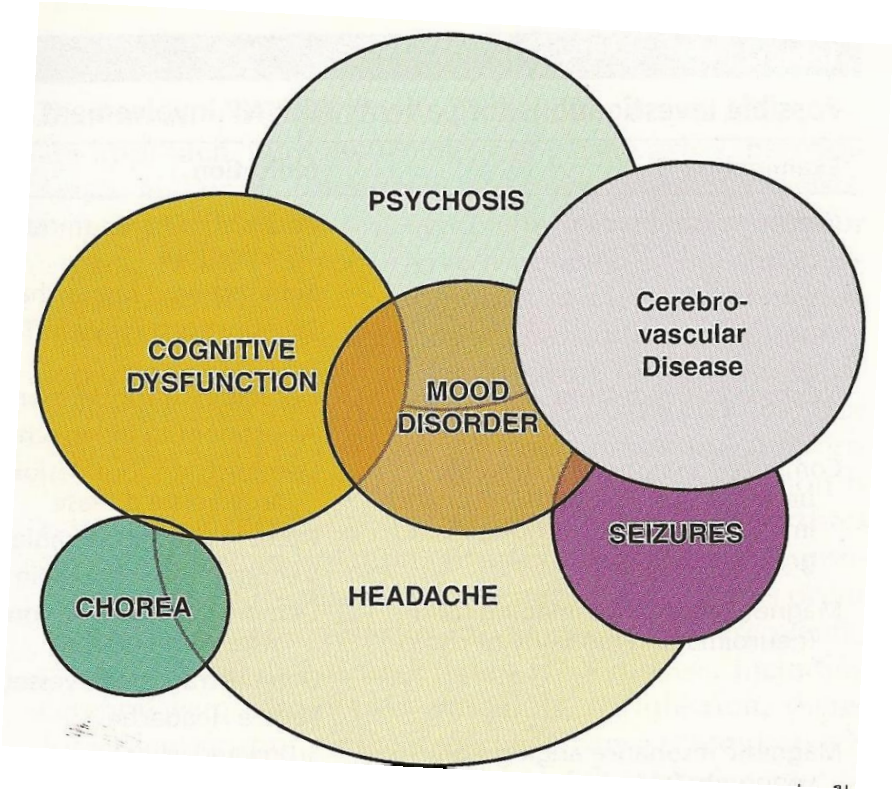


Immunostaining:
IgG, M, A, complement



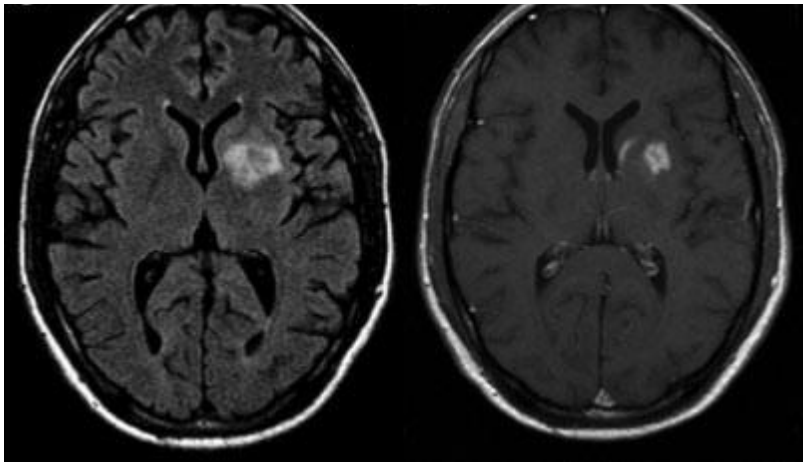
EM: large electron dense deposits in subendothelial region

Neuropsychiatric lupus (NPS)



CNS lupus

- In 25%-90% of patients
- Headache and cognitive disturbance
- Movement disorder – chorea (APL)
- Seizures –
  - Usually focal
  - Intractable/Rasmussens
- Psychosis
- 10-20 % paediatric psychosis
- Mononeuritis/transverse myelitis
- MRI can be normal



Musculo-skeletal disease

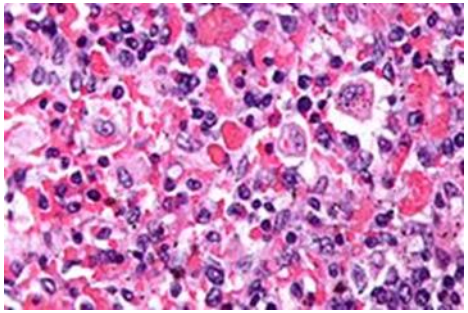
- Arthritis, arthralgia and/or tenosynovitis
- Morning stiffness common
- More than 90% with arthritis develop this within the 1st year of diagnosis
  - so always consider differential diagnosis for those with “late arthritis”
- Deforming arthritis associated with ligament and tendon laxity (Jaccoud arthritis)
- Rhupus: +RF and destructive arthritis

Haematological involvement

- Anaemia
- Coombs positivity
- Thrombocytopenia
- Leucopenia

Macrophage activation syndrome

- Uncontrolled activation of the cellular immune system
- Seen in sJIA, SLE, systemic vasculitis
- Macrophages phagocytose cells in bone marrow
- Falling: ESR, wbc, plats, & fibrinogen
- Very high ferritin
- Bone marrow aspiration may help
- Treatment-IVMP, IV ciclosporin, others



Cardiovascular Findings In SLE

- Pericarditis
- Myocarditis
- Sterile valvular vegetations
- Arrhythmias
- Cor pulmonale
- Vasculitis (small vessels)
- Atherosclerosis/ Coronary Heart disease
- Dyslipidaemia

Pulmonary Findings In SLE

- Incidence: 5-67%
- May be subclinical (abnormal PFTs)
- Pleuritis
- Pleural effusion
- Pneumonitis
- Pulmonary hemorrhage
- Bronchiectasis
- Pulmonary hypertension
- Restrictive lung disease & diffusion defects most commonly observed abnormalities on PFTs

GI INVOLVEMENT IN SLE

- Mild LFT elevation:
  - Exclude autoimmune hepatitis
- Colitis
- Mesenteric vasculitis
- Protein-losing enteropathy
- Pancreatitis
- Exudative ascites

Recommended laboratory investigations for routine (3 monthly) and annual JSLE monitoring (adapted from the UK JSLE Cohort Study)

Routine monitoring (3 monthly)	*Annual testing*
Full blood count (FBC)	Anti-nuclear antibodies (ANA)
Direct coombs test	Extra-nuclear antibodies (ENAs)
Erythrocyte sedimentation rate (ESR)	Lupus anticoagulant
Urea and electrolytes	Thyroid antibodies
C reactive protein (CRP)	Anti-cardiolipin antibodies
Liver function tests	Complement 1q (C1q) antibodies
Immunoglobulins	Creatinine kinase
Complement 3 (C3) and 4 (C4)	Lipid profile
Anti-double stranded DNA titres	Thyroid function tests
Urine sediment/microscopy	
Urine albumin:creatinine ratio	

TA Morgan et al. Lupus 2013;22:1309-1319

LUPUS

Scores of Activity & Damage

- BILAG 2004
- SLEDAI 2000

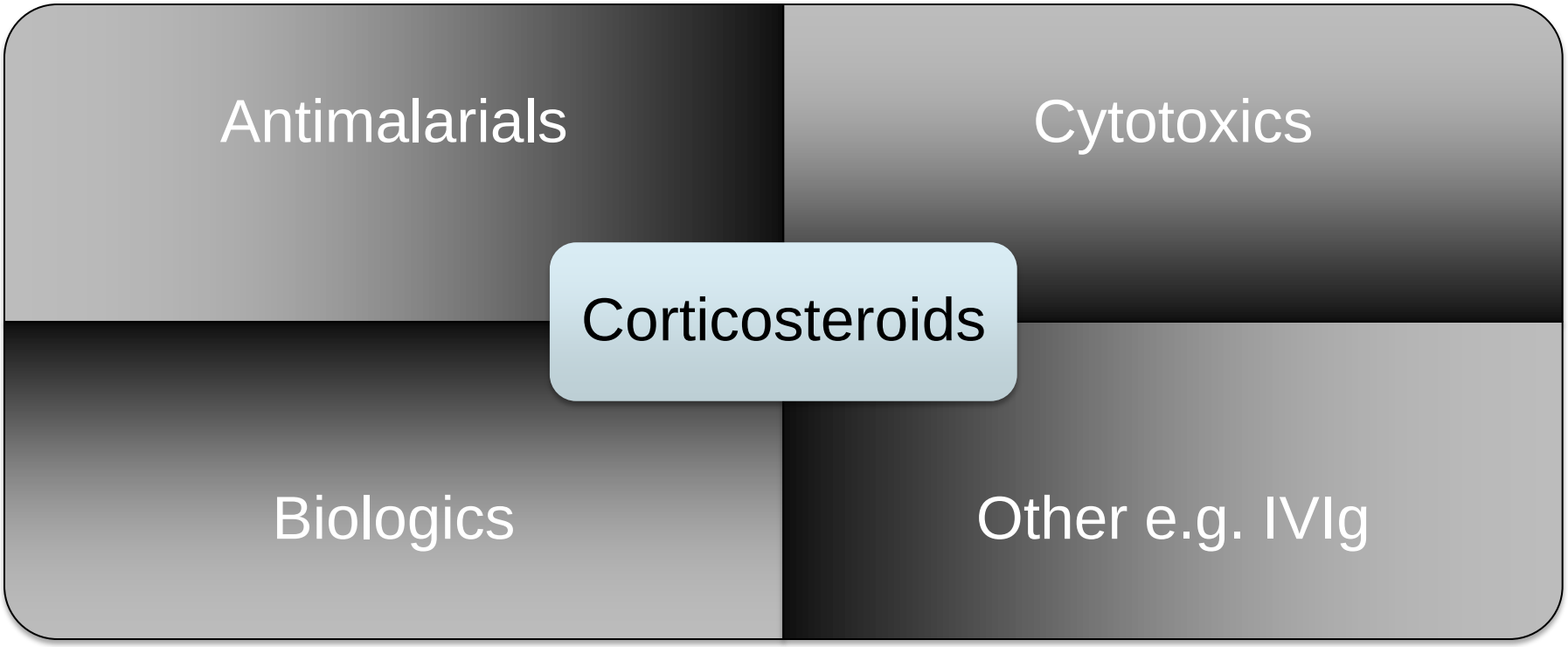
- SLICC/ACR damage index

Management

JSLE - treatment

- Non pharmacological
    - Limit UV exposure
    - Address vitamin D
    - OCP – avoid if aCL / LA positive
    - Issues re vaccination in immunosuppressed
    - Psychosocial issues / adherence

JSLE - treatment



Corticosteroids

Required at some stage by most patients

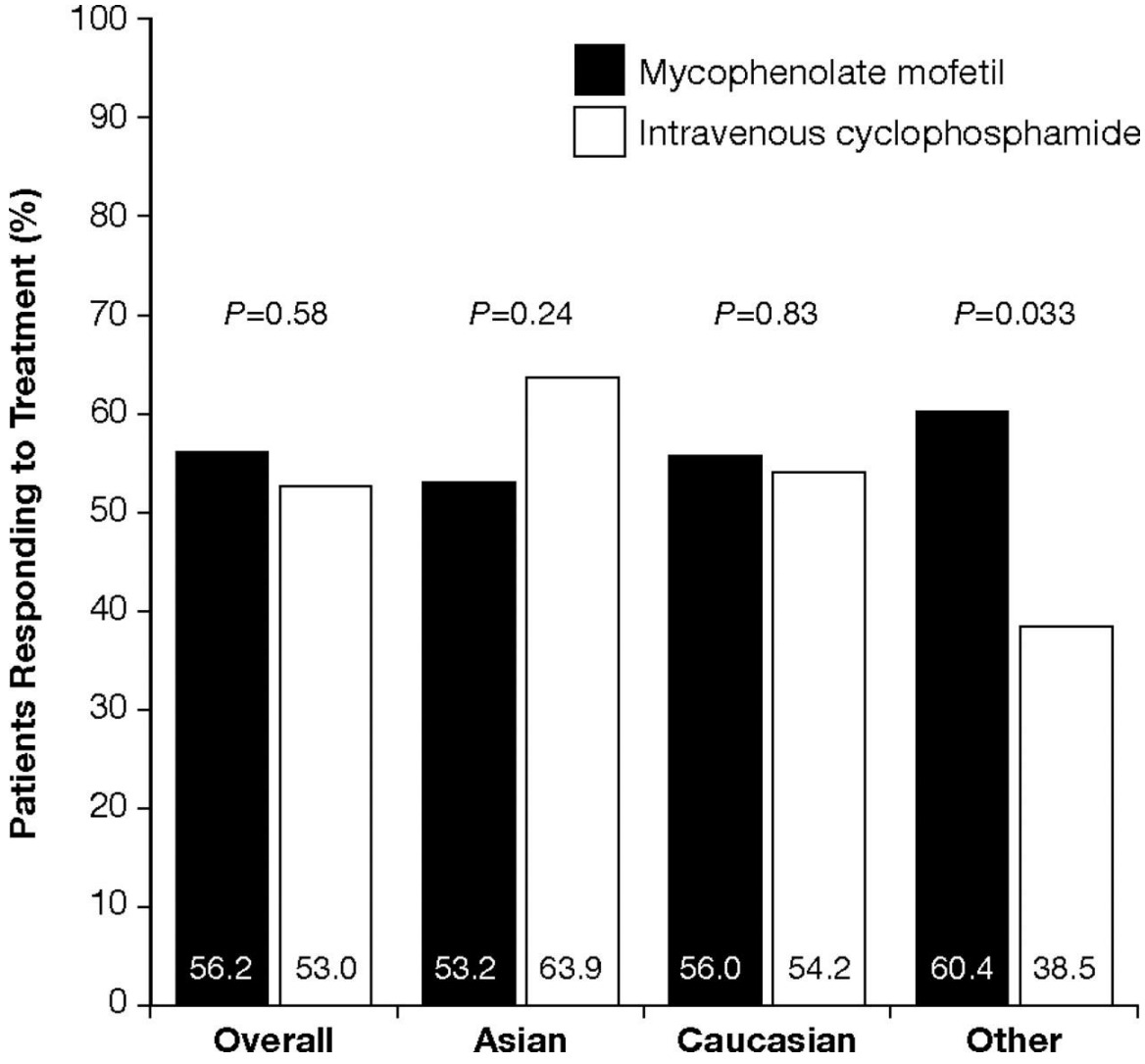
- E.g. 1-2 mg per kilogram/day, then tapered
- Intravenous pulsed methylprednisolone (30 mg/kilogram X 3: “MP3”)

JSLE - treatment

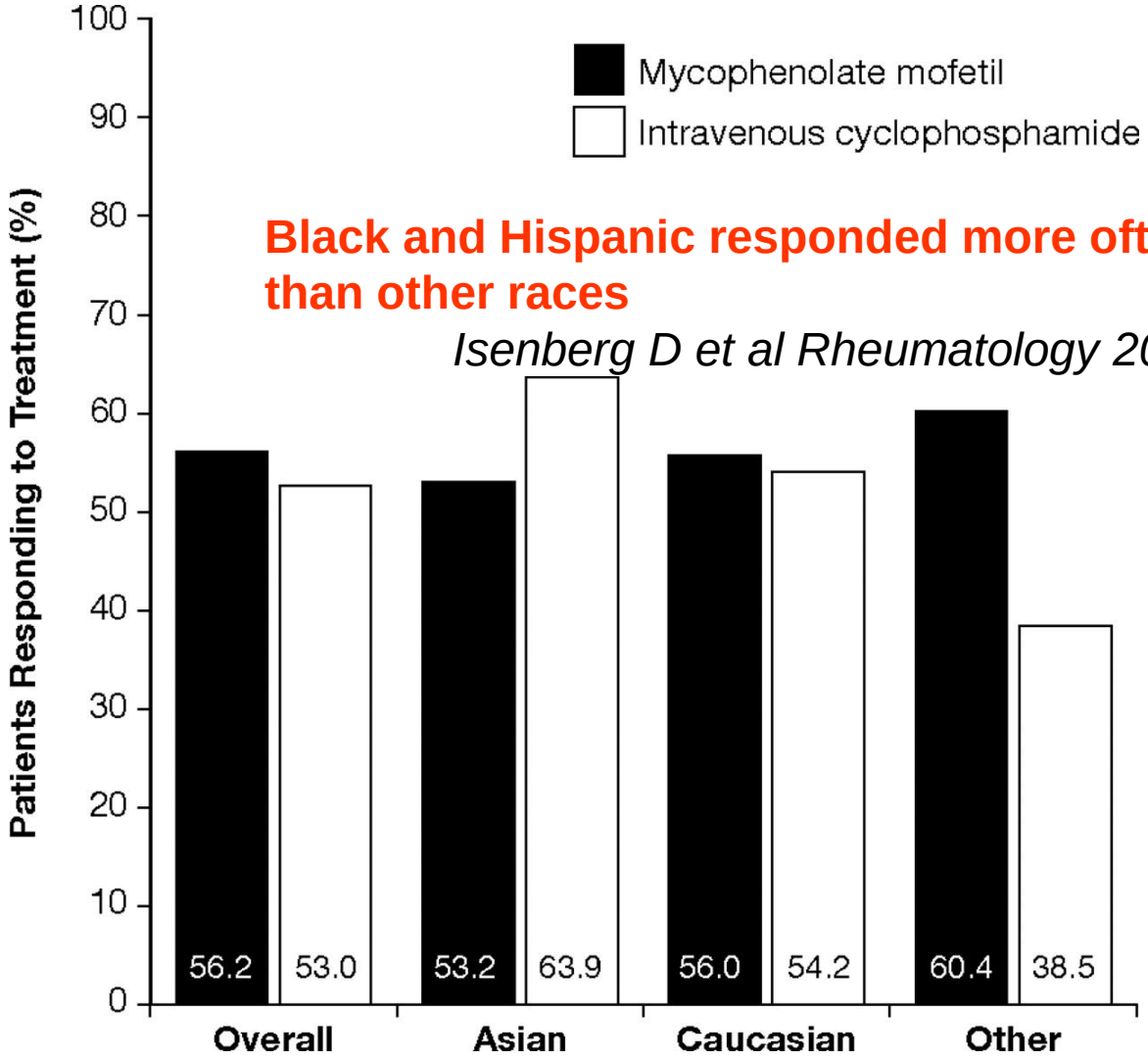
- Hydroxychloroquine 5-6.5 mg/kg/day (200-400mg/day) – skin, joints, fatigue
- Cytotoxics
    - Azathioprine: 1-3 mg/kg/day (max 150 mg/day): moderate SLE
    - Methotrexate: 15 mg/m^2/week (max 25 mg): Joint disease
    - Cyclophosphamide – pulsed IV 500-750 mg/m^2 every 3-4 weeks (max 1.2g): Severe NP-SLE; Class 4 LN?
    - Mycophenolate Mofetil: 600 mg/m^2 twice daily (max 1g BD) (Class 3-5 LN); Moderate-severe SLE)

Lupus nephritis

ALMS results



ALMS results



Black and Hispanic responded more often to MMF than other races

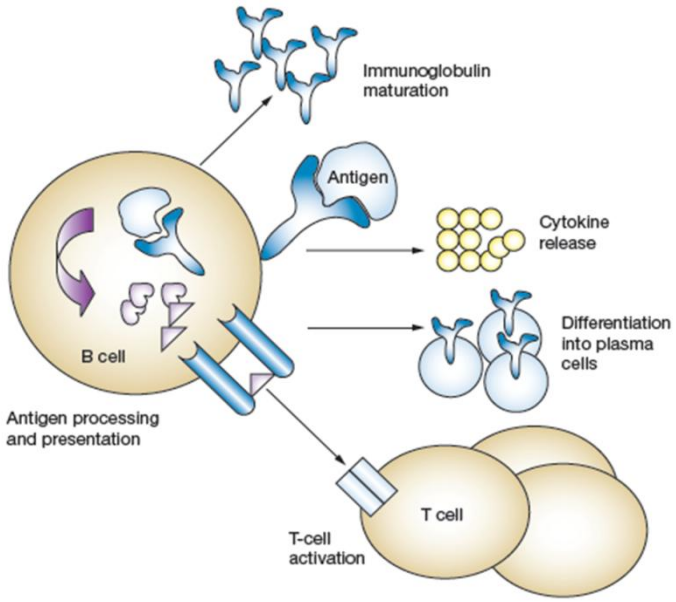
Isenberg D et al Rheumatology 2010;49:128

Rituximab

- Monoclonal antibody
  - binds to CD20 Ag
    - located on pre-B and mature B lymphocytes
    - mediates B-cell lysis

JSLE – Other treatment

- Biologics – B cell depletion therapy
  - Anti-CD20 (Ofatumumab, others..
  - Anti-BlyS (Belimumab)



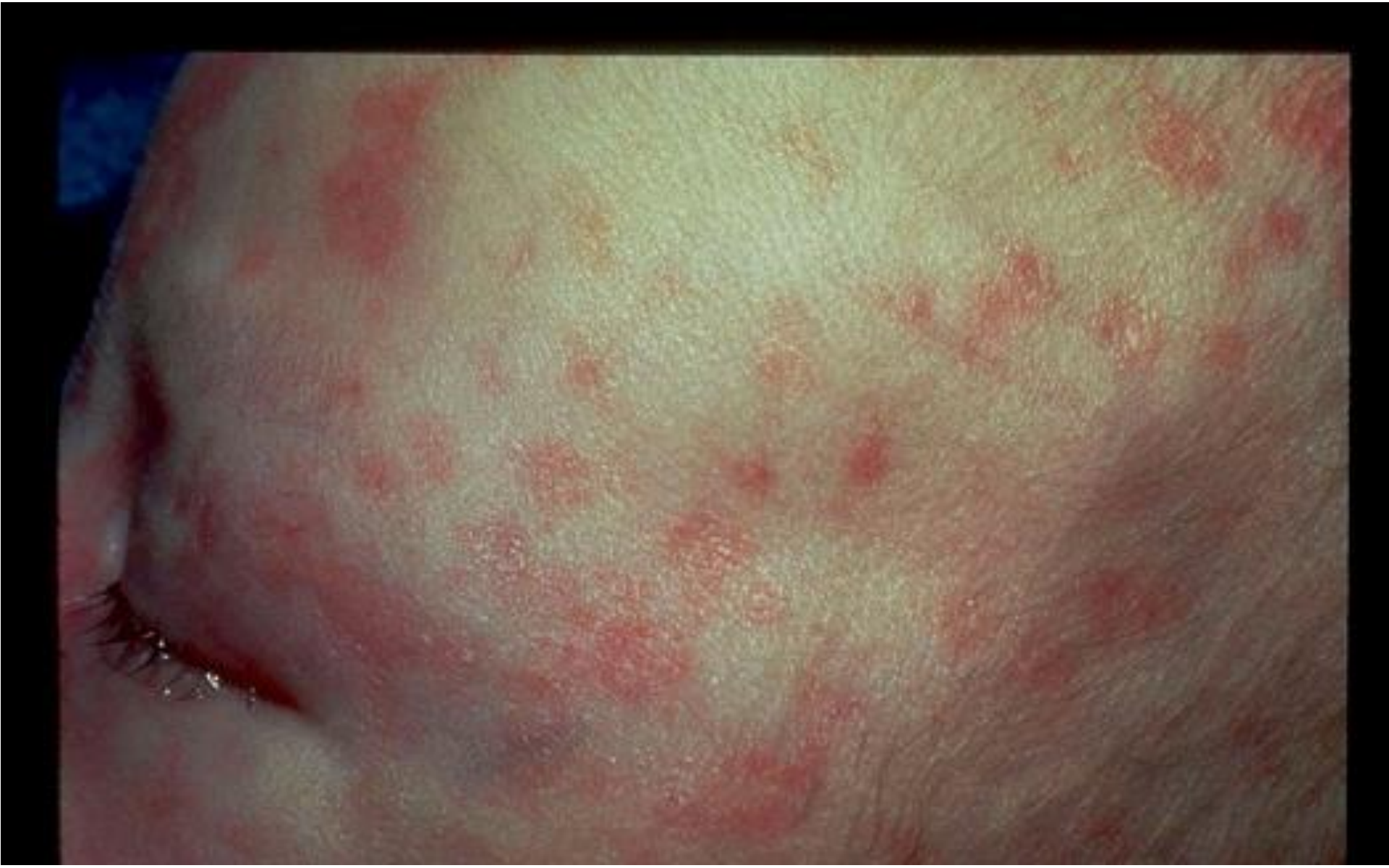
- Other
  - IVIg (thrombocytopenia, myositis, diffuse haemorrhagic alveolitis)
  - Anti-aggregation and anticoagulation for APS
  - Mepacrine – skin
  - Plasma exchange: lung haemorrhage; TTP; severe NP-SLE
  - Autologous Haematopoietic Stem Cell Transplantation

Prognosis

jSLE prognosis

- jSLE survival: 10 year survival approximately 90%
- LN: >90% renal survival
- Cardiovascular disease
  - 6-9 X increase stroke or MI
  - MI rate of 8% in 24-43 year olds who developed SLE in childhood
  - Statins did not influence subclinical measures of atherosclerosis in jSLE over 3 years (APPLE trial)
  - HCQ improves lipid profile
- Bone health: osteopenia in 40%; vertebral fractures in 6-10%

Neonatal lupus



Neonatal lupus

- Born to mothers with Ro/La antibody
  - Risk is 2% to an infant with positive mother
- Clinical features
  - *Skin:* subacute cutaneous lupus-like lesions, telangiectasia.
  - *Cardiac:* **congenital heart block (2%); mortality 15-25%.** Cardiomyopathy, prolonged QT interval, sinus bradycardia, cardiac malformations.
  - *Hepatobilary:* transaminitis, cholestasis, liver failure very rare.
  - *Haematological:* thrombocytopenia and less commonly other cytopenias.
  - Recurrence in a subsequent pregnancy 15%

Neonatal lupus: Treatment/Prognosis

- Careful in utero and postnatal monitoring of at-risk pregnancies is important to ensure appropriate treatment (serial fetal echo; postnatal ECG).
- Use of maternal fluorinated corticosteroids (dexamethasone or beclamethasone) which cross the placenta may prevent progression of incomplete heart block.
- Infants with cardiac disease may need cardiac pacing.
- Skin lesions can be treated with sun avoidance, sun block and topical corticosteroids.

Prognosis

- Skin, hepatic and haematological manifestations tend to resolve spontaneously as maternal autoantibodies disappear from the infant's circulation; complete heart block and cardiomyopathy can be life threatening.
- Affected infants may be at ↑ risk of subsequent autoimmune disease.