Systemic Lupus Erythematosus
&
Lupus Nephritis

Prof. Amr Sarhan

Mansoura University

Objectives

- Systemic lupus Erythematosus

  Problematic and tough medical subject

- Lupus nephritis

  Diagnosis

  Treatment

  Follow up

SLE

- **SLE is *a chronic* inflammatory autoimmune disease**
- **It is *not uncommon*, it's prevalence ranges from 15-80 per 100,000 individuals (about 5 millions patients worldwide). Childhood SLE accounts about 20% of all cases**
- **It's etiology remains *unknown*, although several factors play a role. These factors include genetic, environmental and immunologic factors**

SLE

- **It's pathogenesis is *debatable,* but defective apoptosis and/or loss of immunological tolerances may play a role**
- **Clinically, it is a chronic *multisystem disease* that affecting many organs with *relapsing and remitting course***
- **It's diagnosis needs constellation of clinical, laboratory, and immunological markers *(scoring system)***

SLE

- It is *a life long disease* with marked disability and *serious complications*
- Treatment needs *team work* with many specialty
- Being immune mediated disease treatment is mainly by immunosuppressive drugs *with different modalities*
- *Life long* follow up is mandatory

SLE

- **SLE represents a *problematic and tough* medical subject**

- **During management of SLE, we are confronted by:**
  - **many guidelines**
  - **many protocols**
  - **many scoring systems**
  - **many therapeutic modalities**

- **SLE is the classical example of the problem of :**
  “ information overflow”

SLE

So,

- In may talk today about lupus nephritis, I will be restricted to the protocol of our Nephrology Unit, MUCH


مستشفى الأطفال الجامعي


EXIT


وحدة الكلى الصناعى

MANSOURA UNIVERSITY CHILDREN'S HOSPITAL

Protocols of management of Lupus nephritis in children

Pediatric Nephrology Unit

2021

Lupus Nephritis

- Diagnosis
- Treatment
- Follow up

I- Diagnosis

- **How do you diagnose rheumatic diseases?**

- **Is it lupus?**
  - **Scoring systems**
  - **Antinuclear antibodies (ANA)**

- **Is it lupus nephritis?**
  - **Renal biopsy**

Diagnostic dilemma of rheumatic diseases

- In rheumatic diseases, no single pathognomonic criterion (clinical or lab) is present for diagnosis particular type
- Immunological markers may be positive in absence of rheumatic disease (ANA)
- Immunological markers are positive in different rheumatic diseases (not specific)
- Other diseases (infectious, metabolic, malignant and bone) cause manifestations similar to rheumatic diseases

Diagnosis of rheumatic diseases

- **Diagnosis depends on constellation of:**
  - Clinical manifestations
  - Autoimmune markers
  - Lab and serological tests
  - Imaging studies
  - Tissue pathology

- **Scoring system is usually used for diagnosis**
  - Rheumatic fever …..... Jones criteria
  - Kawasaki disease ……fever for at least 4 days + 4 / 5
  - SLE ……4/11
  - Dermatomyositis
  - Rheumatoid arthritis

Is it lupus?

- **Lupus should be suspect in the following situations?**

  - **Chronic multisystem disease affecting many organs (skin, joints, kidney, CNS, serous membranes ……)**
  - **Unexplained immune-mediated cytopenia (hemolytic anemia, leukopenia, ITP)**
  - **Pyrexia of unknown origin, usually associated with malaise, anorexia, ….**

Is it lupus?

- **Steps of diagnosis**
  - **Exclude non rheumatic diseases**
    - **Infectious, malignant, bone or metabolic diseases**
  - **Positive ANA with significant titer …. (screening test)**
  - **Exclude other connective tissue or rheumatic diseases**
- **Scoring systems for SLE**

Scoring Systems

- American College of Rheumatology
- Systemic Lupus International Collaborative Clinic
- ACR/EULAR

I- Scoring Systems of American Collage of Rheumatology (ACR)

- First ACR scoring system was formulated at 1971
- It was modified at ……1982
- Another modification was done at …… 1997

Mansoura University
Children's Hospital
Nephrology Unit

جامعة المنصورة
مستشفى الأطفال
وحدة أمراض الكلى

1971	1982	1997
1. Facial erythema	1. Malar rash	1. Malar rash
2. Discoid lupus	2. Discoid rash	2. Discoid rash
3. Photosensitivity	3. Photosensitivity	3. Photosensitivity
4. Oral or nasal ulcerations	4. Oral or nasal ulcerations	4. Oral or nasal ulcerations
5. Alopecia		
6. Raynaud's phenomenon		
7. Arthritis without deformity	5. Arthritis: nonerosive arthritis involving two or more joints	5. Nonerosive arthritis: involving two or more joints, characterized by tenderness, swelling or effusion
8. Pleuritis or pericarditis	6. Serositis: pleuritis or pericarditis	6. Pleuritis or pericarditis
9.Proteinuria 10. Cellular casts	7. Renal disorder: persistent proteinuria or cellular casts	7. Renal disorder: persistent proteinuria or cellular casts
11. Psychosis or convulsions	8. Neurologic disorder: seizures or psychosis in the absence of offending drugs or known metabolic derangements	8. Neurologic disorder: seizures or psychosis
12. Hemolytic anemia or leucopenia or thrombocytopenia	9. Hematologic disorder: hemolytic anemia or leukopenia or lymphopenia or thrombocytopenia	9. Hematologic disorder: 1. hemolytic anemia or 2. leukopenia or 3.lymphopenia or 4.thrombocytopenia
13. L. E. cells 14. Chronic false positive test for syphilis	10. Immunologic disorder: positive LE cell preparation or anti-DNA antibody or anti-Sm antibody or false positive test for syphilis	10. Immunologic disorder: 1. anti-DNA antibody to native DNA or 2. anti-Sm antibody or 3. Positive antiphospholipid antibodies : 1) IgG or IgM anticardiolipin 2) positive lupus anticoagulant (LA) or 3) false positive test for syphilis
	11. Positive antinuclear antibody by IFT or an equivalent assay	11. Positive antinuclear antibody by IFT or an equivalent assay

II- Scoring System of Systemic Lupus International Collaborative Clinic

- **Scoring system of SLICC was formulated at 2012**

Mansoura University
Children's Hospital
Nephrology Unit

جامعة المنصورة
مستشفى الأطفال
وحدة أمراض الكلى

2012	2012
Clinical Criteria	*Immunologic criteria*
1. Acute cutaneous lupus	1. ANA level above laboratory reference range
2. Chronic cutaneous lupus	2. Anti-dsDNA antibody level above laboratory reference range
3. Oral or nasopharyngeal ulcerations	3. Anti-Sm presence
4. Nonscarring alopecia	4. Antiphospholipid antibody positive, by any of the following: -medium or high titer anti-cardiolipin -positive test for anti-beta-2-glycoprotein
5. Synovitis involving two or more joints	5. Low complement
6. Serositis	6. Direct Coombs' test in the absence of hemolytic anemia
7. Renal disorder	
8. Neurologic disorder	
9. Hemolytic anemia	
10. Leukopenia or lymphopenia	
11. Thrombocytopenia	

III- Scoring System

- **American Collage of Rheumatology and European Alliance of Association for Rheumatology (ACR/EULAR)**

- **It was formulated at …… 2019**

Mansoura University
Children's Hospital
Nephrology Unit

جامعة المنصورة
مستشفى الأطفال
وحدة أمراض الكلى

New diagnostic criteria of SLE according to ARC/ EULAR 2019

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

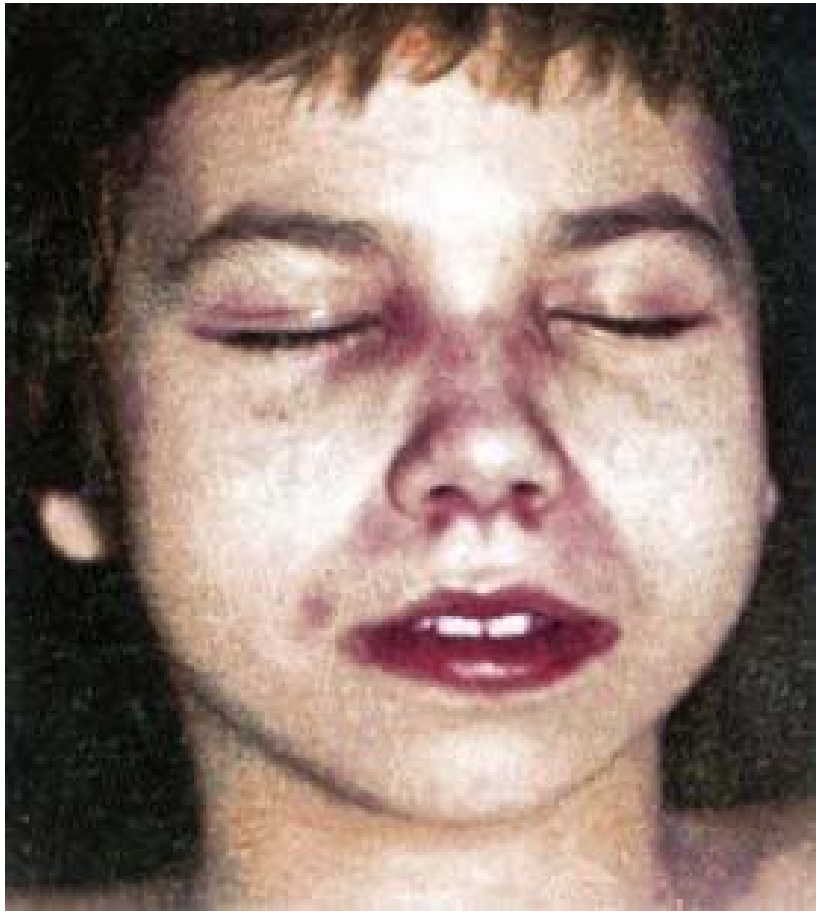
↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Definitions of SLE diagnostic criteria according to EULAR (2019)

Definitions of SLE diagnostic criteria according to EULAR 2019

Criteria	Definition
Antinuclear antibodies (ANA)	ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test at least once. Testing by immunofluorescence on HEp-2 cells or a solid-phase ANA screening immunoassay with at least equivalent performance is highly recommended
Fever	Temperature >38.3°C
Leukopenia	White blood cell count <4,000/mm³
Thrombocytopenia	Platelet count <100,000/mm³
Autoimmune hemolysis	Evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH, AND positive Coombs' (direct antiglobulin) test
Delirium	Characterized by 1) change in consciousness or level of arousal with reduced ability to focus, 2) symptom development over hours (s <2 days), 3) symptom fluctuation throughout the day, 4) either 4a) acute/subacute change in cognition (e.g., memory deficit or disorientation), or 4b) change in behavior, mood, or affect (e.g., restlessness, reversal of sleep/wake cycle)
Psychosis	Characterized by 1) delusions and/or hallucinations without insight and 2) absence of delirium
Seizure	Primary generalized seizure or partial/focal seizure
Non-scarring alopecia	Non-scarring alopecia observed by a clinician†
Oral ulcers	Oral ulcers observed by a clinician†
Subacute cutaneous OR discoid lupus	Subacute cutaneous lupus erythematosus observed by a clinician† Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted). OR Discoid lupus erythematosus observed by a clinician† Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp) leading to scarring alopecia on the scalp If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular and/or periappendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition may be noted)
Acute cutaneous lupus	Malar rash or generalized maculopapular rash observed by a clinician† If skin biopsy is performed, typical changes must be present (interface vacuolar dermatitis consisting of a perivascular lymphohistiocytic infiltrate, often with dermal mucin noted. Perivascular neutrophilic infiltrate may be present early in the course)
Pleural or pericardial effusion	Imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both
Acute pericarditis	≥2 of 1) pericardial chest pain (typically sharp, worse with inspiration, improved by leaning forward), 2) pericardial rub, 3) EKG with new widespread ST elevation or PR depression, 4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI)
Joint involvement	EITHER 1) synovitis involving 2 or more joints characterized by swelling or effusion OR 2) tenderness in 2 or more joints and at least 30 minutes of morning stiffness
Proteinuria >0.5 g/24 hours	Proteinuria >0.5 g/24 hours by 24-hour urine or equivalent spot urine protein-to-creatinine ratio
Class II or V lupus nephritis on renal biopsy according to ISN/RPS 2003 classification	Class II: Mesangial proliferative lupus nephritis: purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy Class V: Membranous lupus nephritis: global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations




Spot
Diagnosis ?

What is ANA?

- Anti nuclear antibodies (> 100 autoantibodies) are the corner stone in pathogenesis and diagnosis of SLE
- It's name is misnomer …... anti-cellular antibodies (cytoplasmic and nuclear)
- It is a screening test for connective tissue diseases .. very sensitive
- It is not specific for particular disease… very non-specific
- It is the stem test for other subtypes

What is ANA?

Mechanism of production

- Defected apoptosis → release of nuclear and cytoplasmic proteins → these proteins are recognized by "antigen presenting cells" → stimulate T-helper cells → activate B-cells which produce unlimited and uncontrolled autoantibodies

Mechanism of action

- Autoantibodies are either:

  Free autoantibodies (type II hypersensitivity reaction)

  Immune complex (type III hypersensitivity reaction)

- Both types are deposited in target tissue → fix complement → Inflammatory reaction → tissue injury and damage

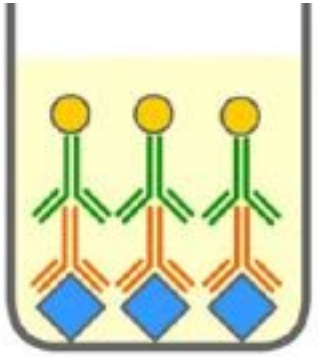
Techniques of assay

Principle

- It is an Immunoassay method that use the ***antigen-antibody reaction*** to *detect* and *quantify* target molecules (antibodies) in biological samples

Method

- **Indirect immunofluorescent (IIF)**
- **Enzyme linked immunosorbent assay (ELISA)**



Titer

- **The standard diagnostic titer is >1/80 by IIF or it's equivalent assay by another method …. ELISA > 20 units**

Subtypes of ANA

- Anti-dsDNA antibodies
- Anti-Smith antibodies .....Stephanie 1966
- Anti-SSA/La
- Anti-SSB/RO
- Others

Is it lupus nephritis ?

- **Lupus nephritis is common in pediatric SLE**
- **About 80% of children with SLE have renal involvement at the onset of disease or during it's course**
- **Renal manifestations are usually in the form of *glomerular touch* (proteinuria, glomerular hematuria, NS, glomerulonephritis, ….)**
- **Renal biopsy is the gold standard for diagnosis of LN**

Renal Biopsy

- When to do?
- Why to do?
- How to interpret?

When to do?

- **Glomerular touch**
  1- Isolated persistent proteinuria >500mg/24h or it's equivalent spot urine / creatinine ratio
  2- Nephrotic syndrome
  3- Persistent glomerular microscopic hematuria

- **Other renal touches**
  1- Persistent hypertension without evidence of vasculitis
  2- Persistent impairment of renal function without apparent cause
  3- AKI with RPGN

why to do?

Renal biopsy is the gold standard for:

- **Confirmation of diagnosis**
- **Classification of renal involvement in LN**
- **Driving treatment decision**
- **Prediction of prognosis**
- **Detection of end organ damage**

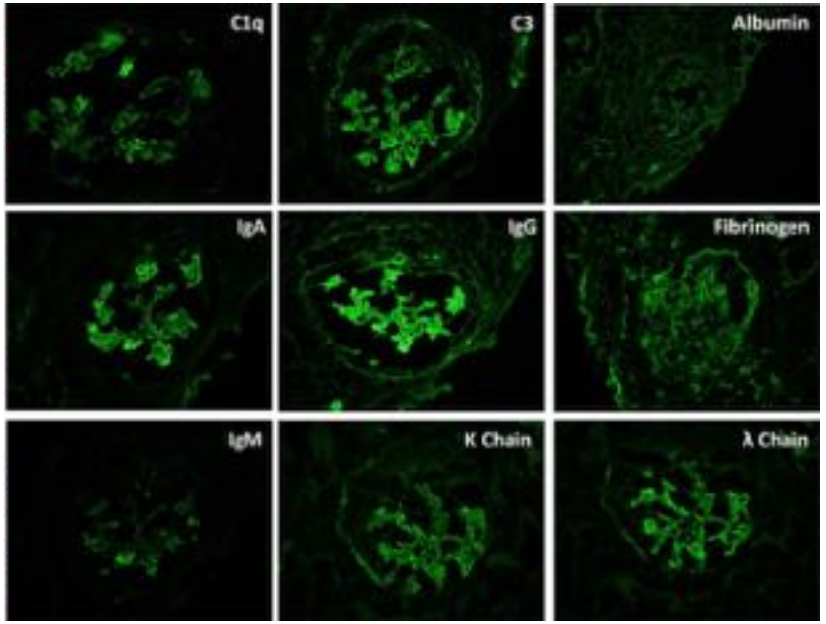
How to interpret ?

- Confirm diagnosis
- Classification of LN
- Activity and chronicity indices
- Evaluation the effect of therapy (2nd look biopsy)
- Non lupus pathological injuries

1- Confirm Diagnosis

- ***Full-house pattern*** of renal biopsy means that all major immunofluorescent stains (IgA, IgM, IgG, C3, C1q …. etc.) are positive by IF microscopic examination

- ***Wire loop appearance*** due to supendothelial deposition of immune complex in class 4 LN



2- Histopathological Classification

- ***WHO Classification***

  It was initially formulated in 1975 and was modified in 1982 and 1995

- **Classification of *International Society of Nephrology and Renal Pathology Society Working Group (ISN/RPS)***

  It was initially done in 2003 and was modified in 2012 and 2018

WHO Classification
1975-1982-1995

WHO Classification of Lupus Nephritis

CLASS I	**Minimal Mesangial Glomerulonephritis** - histologically normal on light microscopy but with mesangial deposits on electron microscopy
CLASS II	**Mesangial Proliferative Lupus Nephritis** - typically responds completely to treatment with corticosteroids
CLASS III	**Focal Proliferative Nephritis** - often successfully responds to treatment with high doses of corticosteroids
CLASS IV	**Diffuse Proliferative Nephritis** - mainly treated with corticosteroids and immunosuppressant drugs
CLASS V	**Membranous Nephritis** - characterized by extreme edema and protein loss
CLASS VI	**Glomerulosclerosis**

ISN/RPS classifications
2003- 2012- 2018

HISTOPATHOLOGICAL CLASSIFICATION OF LUPUS NEPHRITIS

Class I

Minimal Mesangial Lupus Nephritis

- Deposition of imune complexes detectable by immunofluorescence techniques.

Class II

Mesangial Proliferative Lupus Nephritis

- Mesangial hipercelularity of any degree or mesangial matrix expansion with immune deposits detectable by light microscopy.

Class III

Focal Lupus Nephritis

- Active or inactive focal, segmental or global endo/extracapillary glomerulonephritis involving <50% of all glomeruli.
- Manifestations include active lesions (A), chronic inactive lesions (C) or active and chronic lesions (A/C)

Class IV

Diffuse Lupus Nephritis

- Active or inactive diffuse, segmental or global endo/extracapillary glomerulonephritis involving ≥50% of all glomeruli. Subendothelial diffuse immune deposits, with or without mesangial alterations, are common.
- This class is also divided in: diffuse segmental (IV-S), when ≥ 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G), when ≥ 50% of the involved glomeruli have global lesions.
- It can also manifest A, C or A/C lesions.

Class V

Membranous Lupus Nephritis

- Global or segmental subepithelial immune deposition or their morphologic sequelae detectable by light, immunofluorescence or electron microscopy, with or without mesangial alterations.
- It can occur in combination with class III or IV and it can manifest advanced sclerosis.

Class VI

Advanced Sclerosis Lupus Nephritis

- Lupus Nephritis with terminal prognosis.
- 90% of the glomeruli in global sclerosis.

3-Activity and chronicity indices of lupus nephritis (NIH)

Mansoura University
Children's Hospital
Nephrology Unit

جامعة المنصورة
مستشفى الأطفال
وحدة أمراض الكلى

Activity and chronicity scores

ACTIVITY AND CHRONICITY INDICES (NIH)	
Activity Index (0-24):	
- Endocapillary hypercellularity	(0-3+)
- Leucocyte infiltration	(0-3+)
- Subendothelial hyaline deposits	(0-3+)
- Fibrinoid necrosis / karyorrhexis	(0-3+) x 2
- Cellular crescents	(0-3+) x 2
- Interticial inflammation	(0-3+)
Chronicity Index (0-12):	
- Glomerular sclerosis	(0-3+)
- Fibrous crescents	(0-3+)
- Tubular atrophy	(0-3+)
- Interticial fibrosis	(0-3+)

4-Evaluation the effect of therapy

- **At the end of induction therapy to asses the effect of treatment**
- **Detection of irreversible end stage renal damage**
- **After prolonged period (2-3 years) of complete clinical and lab. remission to asses complete cure**

?????

II- Treatment of Lupus Nephritis

Treatment of lupus nephritis

Facts before start treatment

- **SLE is a life long disease with relapsing and remitting course**
- **Treatment of LN needs team work (nephrology, neurology, psychiatry, rheumatology, nutrition, social worker …)**
- **Target of treatment is to maintain remission with minimal dose and safest modality of immunosuppressive therapy**
- **Choice of treatment modality is a balance between control of disease activity and possible complications of immunosuppressive therapy**

Treatment of lupus nephritis

- **There are few randomized controlled trails (RCT) to guide treatment of children with LN**
- **Most protocols used in treatment of children with LN are derived from adult studies**
- **Several concerns should be addressed when treating children with LN**
  - ***Compliance to medication***
  - ***Infertility***
  - ***Growth failure***
  - ***Psychosocial concern***
  - ***Aggressive course of LN***

Standard Treatment of Lupus Nephritis class III & IV

- Induction therapy to control acute stage of disease, it includes :

  1- Methyl pred. IV daily for 5 days

  2- Oral prednisolone 1mg/kg/24h

  3- Cyclophosphamide IV/ monthly for 6 months

  4- MMF oral for 6 months ..... female > 16 years old

- Maintenance therapy to maintain control of activity

  1- Cyclophosphamide IV/ 3 months for18 months

  2- MMF oral for 2-3 years

Refractory Lupus Nephritis

- Definition:
  - Failure to achieve complete or partial response within 6-12 months of starting induction therapy or worsen of clinical and/or laboratory manifestations

- Treatment
  - It is achieved by more potent immunosuppressive drugs
  - The choice of treatment modality is guided by the severity of clinical manifestations and non lupus pathological injuries

Non-lupus pathological injuries

- Vascular injuries
- Podocyte injuries
- Crescentic injurie
- Tubulointerstitial injuries

Vascular injuries

- **Mechanism**
  - **Deposition of immune complex in vascular smooth muscle cells leading to vasculitis and thrombotic microangiopathy (TMA)**
- **Clinically**
  - **HUS, Hypertension, dyslipidemia, thromboembolism**
- **Treatment**
  - **Eculizumab or plasma exchange**

Podocyte injuries

- **Mechanism**
  - **Loss expression of slit diaphragm proteins (nephrin and podocin) leading to effacement of foot process that is detected by EM**
- **Clinically**
  - **Marked proteinuria and nephrotic syndrome**
- **Treatment**
  - **Calcineurin inhibitors (cyclosporin or prograf)**

Crescentic injuries

- **Mechanism**
  - **Deposition of immune complex in epithelial lining of Bowman's capsule leading to crescentic nephritis**
- **Clinically**
  - **RPGN associated with ANCA positive antibodies**
- **Treatment**
  - **Plasma exchange**
  - **Endoxan if not exceed maximum therapeutic level or not be taken during induction therapy**

Tubulointerstitial injuries

- **Mechanism**
  - Clonal expansion of B-cells and plasma cells
  - Over production of autoantibodies
  - Deposition of immune complex along tubular basement membrane
  - Inflammatory response leading to tubulointerstitial nephritis

- **Treatment**
  - B-cells depletion therapy (rituximab)

Non-immunosuppressive treatment

- Protective measurements
  - Avoid direct sun exposure, drug induced lupus
- Control proteinuria
  - ACEIs and/or ARBs
- Hydroxychloroquine

  Hydroquine …4-6 mg/kg /24h

  Fundus examination every year

Non-immunosuppressive treatment

- **Dyslipidemia**
  - Diet and exercise
  - Pharmacological treatment

    statins

    cholestyramine

Thromboembolic complications

Screening for anti-phospholipid antibodies if +ve :

Primary prophylaxis …. (antiplatelet)

Secondary prevention … (anticoagulants)

- **Hypertension control**

Non-immunosuppressive treatment

- Osteopenia
  - Annual DEXA scan
  - Vit D and calcium supplementation
- Immunization and management of infections
- Replacement therapy in ESRD

  Dialysis or transplantation

III- Follow up

Follow up

Facts before planning of follow up

- Follow up of children with LN is life long
- Regular follow up for mild and stable cases is done every 3 months
- In severe cases, follow up is done more frequent
- In more sever cases, patients need hospital admission
- …….

Follow up

Target of follow up:

- ***Diagnosis of lupus flare (SLEDAI Score)***
  - **Renal flare (nephritic, nephrotic, ….)**
  - **Extra renal flare (vasculitis, hematological, neurological, skin ..)**

- ***Detect Complications of both disease and medications***
  - **Infections, thromboembolic events, CVD, eye,**

- **Detect end organ damage**

Follow up

Can a lupus flare be predicted?

- The answer is no
- No single predictive marker for lupus flare has yet been identified
- Raised titer of anti dsDNA and/or decrease serum level of C3 and C4 are usually associated with flare

Follow up

So, during routine follow up, patients with SLE should be monitored for:

- Clinical manifestations of disease activity (flare)
- Lab. findings of disease activity (CBC, C3, autoantibodies urine analysis, kidney function ...)
- Complications of disease and drugs used (high level of suspicious)
- Detection of irreversible organ damage

Follow up

Can lupus flare be measured?

- **The answer is yes**
- **Measurement is done by SLE Disease Activity Index**

  "SLEDAI 2K Score 2002"

  It measures disease activity in last 30 days

  It's range from 0-105

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI Score)

Mansoura University
Children's Hospital
Nephrology Unit

جامعة المنصورة
مستشفى الأطفال
وحدة أمراض الكلى

SLE Disease Activity Index (SLEDAI)

SLEDAI-2K (30 DAYS)
DATA COLLECTION SHEET

Study No: Patient Name: Visit Date: d/ m/ yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 30 days)

Weight	SCORE	Descriptor	Definition
8	☐	Seizure	Recent onset, exclude metabolic, infections, or drug causes
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	☐	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	☐	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	☐	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
8	☐	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	Arthritis	>2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary casts	Heme-granular or red blood cell casts
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other cause.
4	☐	Proteinuria	>0.5 gram/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	Rash	Inflammatory type rash.
2	☐	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	☐	Mucosal ulcers	Oral or nasal ulcerations.
2	☐	Pleurisy	Pleuritic chest pain with pleural rub or effusion or pleural thickening.
2	☐	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	☐	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	☐	Fever	>38° C. Exclude infectious cause.
1	☐	Thrombocytopenia	<100,000 platelets/= 10^9/L, exclude drug causes.
1	☐	Leukopenia	<3000 white blood cells/= 10^9/L, exclude drug causes.

Conclusions

Conclusions

- SLE is an autoimmune chronic inflammatory disease
- It is a long life disease with relapsing and remitting course
- Diagnosis depends on constellation of clinical manifestations and autoimmune markers
- Scoring system is usually used for diagnosis

Conclusions

- Diagnosis of lupus nephritis and it's pathological class is a corner stone in management and prognosis of SLE
- Plane for appropriate therapy depends on type and severity of disease activity and class of renal pathology
- Choice of treatment is a balance between control of disease activity and possible complications of immunosuppressive therapy

Thank you

WHO Classification of Lupus Nephritis

CLASS I	**Minimal Mesangial Glomerulonephritis** - histologically normal on light microscopy but with mesangial deposits on electron microscopy
CLASS II	**Mesangial Proliferative Lupus Nephritis** - typically responds completely to treatment with corticosteroids
CLASS III	**Focal Proliferative Nephritis** - often successfully responds to treatment with high doses of corticosteroids
CLASS IV	**Diffuse Proliferative Nephritis** - mainly treated with corticosteroids and immunosuppressant drugs
CLASS V	**Membranous Nephritis** - characterized by extreme edema and protein loss
CLASS VI	**Glomerulosclerosis**

NIH activity index	Modified NIH activity index	Score
1. Endocapillary proliferation	1. Endocapillary hypercellularity	0 – 3
2. Glomerular leucocyte infiltration	2. Neutrophils and/or karyorrhexis	0 – 3
3. Fibrinoid necrosis/karyorrhexis	3. Fibrinoid necrosis	(0 – 3) x 2
4. Hyaline deposits	4. Hyaline deposits	0 – 3
5. Cellular crescent	5. Cellular and/or fibrocellular crescents	(0 – 3) x 2
6. Interstitial inflammation	6. Interstitial inflammation	0 – 3
Total		0 – 24

NIH chronicity index	Modified NIH chronicity index	Score
1. Global sclerosis	1. Total glomerulosclerosis score	0 – 3
2. Fibrous crescents	2. Fibrous crescents	0 – 3
3. Tubular atrophy	3. Tubular atrophy	0 – 3
4. Interstitial fibrosis	4. Interstitial fibrosis	0 – 3
Total		0 – 12

SLEDAI-2K score	Descriptor	Definition
8	**Seizure**	Recent onset, exclude metabolic, infectious or drug causes.
8	**Psychosis**	Altered ability to function in normal activity due to severe disturbance in the perception of reality.
8	**Organic brain syndrome**	Altered mental function with impaired orientation, memory or other intellectual function.
8	**Visual disturbance**	Retinal changes.
8	**Cranial nerve disorder**	New onset of sensory or motor neuropathy involving cranial nerves.
8	**Lupus headache**	Severe, persistent headache which may be migrainous, but must be nonresponsive to narcotic analgesia.
8	**Cerebrovascular accident**	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	**Vasculitis**	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter haemorrhages, or biopsy or angiogram proof of vasculitis.
4	**Arthritis**	≥2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion).
4	**Myositis**	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or biopsy showing myositis.
4	**Urinary casts**	Heme granular or red blood cell casts.
4	**Haematuria**	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	**Proteinuria**	>0.5 gram/24 hours.
4	**Pyuria**	>5 white blood cells/high power field. Exclude infection.
2	**Rash**	Inflammatory type rash.
2	**Alopecia**	Abnormal, patchy or diffuse loss of hair.
2	**Mucosal ulcers**	Oral or nasal ulcerations.
2	**Pleurisy**	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	**Pericarditis**	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	**Low complement**	Decrease in CH50, C3 or C4.
2	**Increased DNA binding**	Increased DNA binding by Farr assay.
1	**Fever**	>38°C. Exclude infectious cause.
1	**Thrombocytopenia**	<100 000 platelets / $x10^9$/L, exclude drug causes.
1	**Leukopenia**	<3000 white blood cells / $x10^9$/L, exclude drug causes.

C3 = Complement protein 3, C4 = Complement protein 4, CH50 = 50% haemolytic complement activity, DNA = deoxyribonuclease, SLEDAI-2K = SLE disease activity index 2000

Summarized from *Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29:288-91* (99).

Treatment of lupus nephritis

- Facts before start treatment

- SLE is a long life disease with relapsing and remitting course

- Treatment of LN needs team work (nephrology, neurology, psychiatry, rheumatology, nutrition, social worker …)

- Target of treatment is to maintain remission with minimal dose and safest modality of immunosuppressive therapy

- Choice of treatment modality is a balance between control of disease activity and possible complications of immunosuppressive therapy

Treatment of lupus nephritis

- Facts before start treatment

- There are few randomized controlled trails (RCT) to guide treatment of children with LN

- Most protocols used in treatment of children with LN are derived from adult studies

- Several concerns should be addressed when treating children with LN
  - Compliance to medication
  - Infertility
  - Growth failure
  - Psychosocial concern
  - Aggressive course of LN

Standard Treatment of Lupus Nephritis class III & IV

- Induction therapy to control acute stage of disease, it includes :
  1- methyl pred. IV daily for 5 days
  2- oral prednisolone
  3- Cyclophosphamide IV/ monthly for 6 months
  4- MMF oral for 6 months … female > 16 years old

- Maintenance therapy to maintain control of activity
  1- Cyclophosphamide IV/ 3 months for18 months
  2- MMF oral for 2-3 years

Refractory Lupus Nephritis

Non-immunosuppressive treatment

- Dyslipidemia
  - Diet and exercise
  - pharmacological treatment
    - statins
    - cholestyramine
- Thromboembolic complications
- Hypertension

Non-immunosuppressive treatment

- Protective measurements

  Avoid direct sun exposure, drug induced lupus

- Control proteinuria

  Avoid high sodium intake

  ACEIs and/or ARBs

- Osteopenia

  Annual DEXA scan

  Vit D and calcium supplementation

Non-immunosuppressive treatment

- Immunization and management of infections
- Replacement therapy

Introduction

- **SLE is a chronic inflammatory autoimmune disease affecting multiple organs**
- **It is not uncommon, it's prevalence ranges from 15-80 per 100,000 individuals (about 5 millions patients worldwide)**
- **Childhood SLE accounts about 20% of all cases**
- **Compared with adults, the consequence of childhood SLE is usually more sever and more organ involvement**

Introduction

- **Pathogenesis**

1- Defective apoptosis leads to release of cellular contents (cytoplasmic and nuclear materials) that act as antigens

2- Antigen presenting cells will recognize these antigens → activate T- helper cells → activate B-cells → plasma cells → produce uncontrolled, unlimited and persistent autoantibodies

Introduction

Etiology

The etiology of SLE remains unknown, but several factors play a role, these factors include:

- **Genetic factors**

  Genetic susceptibility but without clear marker

- **Environmental factors**

  Hormones, drugs, infections (EBV), sun exposure

- **Immunologic factors**

  Persistent and uncontrolled activation of *B* lymphocytes that produce unlimited autoantibodies

Introduction

3- These autoantibodies combined with corresponding antigens and form Immune complexes

4- These autoantibodies and immune complexes are deposited at target tissue and activate complement system

5- Inflammatory reaction occurs leading to tissue injury and damage of multiple organs

Technique of assay