Clinical immunology, Part 1

Systemic autoimmune diseases:

Systemic Lupus Erythematosus (SLE)

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Lecture outline

- **Immunology / immune system**: concepts, functions
- **Self-tolerance**: significance, mechanisms
- **Autoimmunity**: definition, paradoxes
- **Autoimmune diseases**: characteristics, etiology patterns, clinical features
- **SLE**
  - epidemiology
  - aspects of etiopathogenesis
  - clinical manifestations
  - diagnosis / criteria, differential diagnosis
  - management, therapeutic approaches
  - prognosis
WHAT IS IMMUNOOLOGY ?
Functions of the immune system

- **Traditional concept:** *immune defense*
  *protection* against infections

- **Immune homeostasis:**
  *discrimination of self and non-self (foreign) antigens with* *tolerance to self* components
  *preservation* of individual antigenic identity
  *clearance* of injured or senile cells, tissue repair

- **Immune surveillance:**
  *prevention* of persistent infections
  *destruction* of transformed (tumor) cells
Aspects of clinical immunology

* disorders of the immune system
  
  failure:  *immunodeficiencies
  aberrant reactions:  *allergic diseases
  *autoimmune diseases
  uncontrolled cell growth:  *lymphoid malignancies

* disorders of other systems  (where immune reactions play a significant part in pathophysiology)

  *infections and immunity
  *cancer immunology
  *transplantation immunology
  *reproductive immunology
Importance of immune regulation

- **To avoid** excessive lymphocyte activation and tissue damage during normal protective responses against infections

- **To prevent** inappropriate reactions against self antigens (i.e. to maintain self-tolerance)

*Failure of control mechanisms is the main underlying cause of immune-mediated inflammatory (autoimmune) diseases*
HOW TO MAINTAIN SELF-TOLERANCE AND PREVENT AUTOIMMUNITY?
**Immune tolerance**

**Definition:**
- specific immune unresponsiveness to a ( tolerogenic) antigen that is induced by exposure of lymphocytes to that antigen

**Significance:**
- all individuals are tolerant to their own antigens ( „self-tolerance” )
- breakdown / failure of self-tolerance-maintaining mechanisms results in autoimmune disease
Autoimmunity

- **Definition**: an immune response against self (auto-) antigen
- **Caution (!)**: autoimmune responses do not necessarily imply the pathologic condition of autoimmune disease

- **Significance - paradoxes:**
  - early idea: any forms of autoimmunity: aggressive!
  - present days: natural autoimmunity: physiologic
    - permanent, immunoregulatory
    - non-self-destructive immune reactivity
      (for providing self-identification and preservation)
    - complex interconnected network of natural autoantibodies
CD5+ B1 cells: produce natural autoantibodies, reactive with conserved, essential molecules

*heat shock proteins (hsp)*  
*enzymes (CytC, SOD)*  
*plasma proteins (albumin, IgG)*  
*membrane proteins (β2 M)*  
*cytoplasmic proteins (actin)*  
*nuclear antigens (DNA, histones)*  
*cytokines, hormones*
### Characteristics of autoreactive antibodies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Natural</th>
<th>Pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum titre</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Affinity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Isotype</td>
<td>IgM&gt;IgG&gt;IgA</td>
<td>IgG&gt;IgM&gt;IgA</td>
</tr>
<tr>
<td>Antigen specificity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>V-region</td>
<td>Germline</td>
<td>Somatic mutations</td>
</tr>
</tbody>
</table>
Pathologic autoimmunity: how does tolerance break down?

A Molecular mimicry
- Infectious agent
- Pathogen-peptide mimicking self-antigen
- Activation of cross-reactive T cells and B cells
- Self-tissue damage

B Protein changes, cryptic antigens
- Infectious agents
- Cryptic epitope presentation
- Modified self-protein presentation
- Activation of self-reactive cells
- Tissue injury, cell death
- Oxidative stress, free radical production

C Superantigens (T cell bypass)
- Infectious agents
- Pathogen superantigens
- Non-specific TCR binding
- Specific TCR binding
- Activation of self-reactive T cells
- Self-tissue damage

D Bystander activation (epitope spreading)
- Infectious agents
- Antigen non-specific activation
- Bystander self-reactive T cell
- Tissue damage, apoptosis
- Activation of self-reactive T cells
AUTOIMMUNE DISEASES
**Definition of AD**: chronic disabling diseases resulting from immune responses against self antigens with prominent inflammation and tissue damage

- affect ~ 5-7% of the world population
- include over 120 conditions
- one of the „top ten” leading causes of death
- patterns: organ-specific, non-organ-specific / systemic

**General shared characteristics:**

- pathogenesis: multifactorial
- familial clustering
- gender, age of onset
- polyautoimmunity
- response to immunosuppressive treatment
AD: multifactorial

Infective agents, hormones, UV-light, dietary factors, drugs, chemicals, stress, etc.

Nature Immunology, 2001
AD: genetics

Mainly polygenic!

Analyses: gene expression profiling, linkage analysis, candidate gene studies, GWAS (microarrays / SNPs)

- higher concordance rates of AD in monozygotic twins
- familial clustering
- frequency of risk alleles may vary by regions, ethnicities
- some polymorphisms are associated with multiple diseases
- some are disease-specific
- inheritance of susceptibility (MHC / non-MHC genes)
  * genetic polymorphism
  * differential gene penetrance in F/M
  * genetic heterogeneity among populations
  * epistasis
**Epigenetics**

**Definition:** stable, heritable or acquired modifications of DNA without alterations in DNA sequence

**Checkpoints:**
- DNA methylation
- histone modifications
- microRNA

Epigenetic changes can switch genes on/off and determine which proteins are transcribed; missing link between genomics and environment in determining phenotype variability of autoimmune diseases
AD: factors of immune pathomechanism

- Fundamental problem: imbalance between immune activation and control

- Nature of diseases is determined by the type of dominant immune response (Th1, Th2, Th17)

- Most of the diseases are chronic and self-perpetuating
Balancing lymphocyte activation and control

Activation effector T cells

Normal: reactions against pathogens
Pathologic: reactions against self

Tolerance regulatory T cells

No response to self
Controlled response to pathogens
Recognition of self antigens

active “NO”
“I see it but I do not react to it”

immune tolerance

active “YES”
“I see it and I react to it”

autoimmune disease
Summary of AD pathomechanism

Susceptibility genes

- Failure of self-tolerance

  - Persistence of functional self-reactive lymphocytes

Epigenetic changes

Environmental triggers
(e.g. infections, tissue injury, etc.)

- Activation of APCs

  - Activation of self-reactive lymphocytes

Immune responses against self tissues

Target organ: inflammation, irreversible damage
Koch-Witebsky’s criteria

How to recognize autoimmune disease?

- **Direct evidence** of causality: an autoimmune response can be shown to produce the disease by
  - transfer of autoantibody /autoreactive T cell from a patient to a healthy recipient

- **Indirect evidence**
  - availability of an appropriate animal model
    - reproduction of the disease in animals via immunization with the appropriate autoantigen
    - naturally occurring disease in animals that resembles its human counterpart

- **Circumstantial evidence**
  - presence of autoantibodies
    - levels reflect disease activity
  - reduction of the autoimmune response leads to disease improvement
Symptoms and signs suggestive for systemic autoimmune disease

- fatigue, malaise, weight loss, low-grade fever
- muscle and/or joint pain
- muscle weakness
- swollen glands, hepato-splenomegaly
- recurrent rashes or hives
- Raynaud’s phenomenon
- photosensitivity
- hair loss
- dry eyes, mouth
- recurrent miscarriages
- nephritis, nephrosis
- numbness or tingling in the hands or feet
- anaemia, leukopenia, thrombocytopenia
- increased ESR, high CRP, polyclonal gamma-globulinemia
Systemic autoimmune diseases

„immune-mediated inflammatory diseases”
„autoimmune rheumatic diseases”
„connective tissue diseases”

- ubiquiter autoantigens
- several affected organs
- acute /subacute inflammation
- destruction of the target organ
- variable clinical manifestations
- disease course: relapsing / remitting
- „marker” autoantibodies
Main types of systemic autoimmune diseases

- systemic lupus erythematosus (SLE)
- rheumatoid arthritis (RA)
- Sjögren’s syndrome (SS)
- (progressive) systemic sclerosis (PSS)
- inflammatory myopathies (poly/dermatomyositis, PM/DM)
- mixed connective tissue disease (MCTD)
- systemic (necrotizing) vasculitides
- antiphospholipid syndrome (APS)
- seronegative spondylarthritides (SNSA)
- relapsing polychondritis
- undifferentiated autoimmune syndromes
- overlap syndromes
SLE: „THE GREAT IMITATOR”
  - T / B /DC cell overactivation, characteristic autoantibodies
  - immune complex production, deposition

Heterogenous
  - variable onset, clinical expressions
  - several clinical subsets
  - variable disease course and prognosis

Epidemiology (adults)
  - prevalence: 20-150 cases /100.000
  - incidence rate: 1-25/100.000/yr
  - familial aggregation
  - geographic/racial distribution: Asians, Afric.-Americans>Caucasians
  - urban > rural areas
  - gender: F / M ~ 9-10 / 1
  - age of onset: 16-55 yrs. (65 %), < 16 yrs (20 %), > 55 yrs. (15 %)
SLE: multifactorial etiology

- Genetics
- Environmental factors
  - infections (EBV !)
  - UVB light
  - smoking
  - dietary factors
  - vitamin D
  - silica dust
  - drugs, chemicals
- Hormonal factors
  - OE (contraceptives / HRT)
  - PRL
- Failure of immune regulation
- Epigenetics
SLE: chromosome loci and associated genes

1. C1q

6. MHC-II: HLA-DR2 (DRB1*1501)
   HLA-DR3 (DRB1*0301)

MHC-III: C4, C2


- Dendritic-cell function and IFN signaling
  - IRF5, STAT4, SPP1, IRAK1, TREX1,
  - TNFAIP3, TNIP1, PRDM1, PHRF1, TYK2,
  - SLC15A4, and TLR8

- Immune-complex processing and innate immunity
  - ITGAM, C1QA, C2, C4A, C4B,
  - FCGR2A, FCGR3A, FCGR3B, KLK1/3,
  - KLRG1, and KIR2DS4

- Other genes
  - PXK, ICA1, XKR6, and SCUBE1

- T-cell function and signaling
  - PTPN22, TNFSF4, PDCD1,
  - IL10, BCL6, IL16, TYK2, PRL,
  - STAT4, and RASGRP3

- B-cell function and signaling
  - BANK1, BLK, LYN, BCL6,
  - and RASGRP3

- Cell cycle, apoptosis, and cellular metabolism
  - CASP10, NMNAT2, PTTG1, MSH5,
  - PTPRT, UBE2L3, ATG5, and RASGRP3

- Transcriptional regulation
  - JAZF1, UHRF1BP1, BCL6,
  - MECP2, ETS1, and IKZF1

- SLE-associated locus
## SLE: identified epigenetic alterations

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Target</th>
<th>Cell Type</th>
<th>Alteration</th>
<th>Consequence</th>
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</thead>
<tbody>
<tr>
<td><strong>DNA methylation</strong></td>
<td>ITGAL (CD11a)</td>
<td>CD4 T cells</td>
<td>Hypomethylation</td>
<td>Increased CD11a expression</td>
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<tr>
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<td>CD70 (TNFSF7)</td>
<td>CD4 T cells</td>
<td>Hypomethylation</td>
<td>Increased CD70 expression and B-cell costimulation</td>
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<tr>
<td></td>
<td>CD154 (CD40L)</td>
<td>CD4 T cells</td>
<td>Hypomethylation</td>
<td>Increased B-cell costimulation</td>
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<td>Perforin</td>
<td>CD4 T cells</td>
<td>Hypomethylation</td>
<td>Increased perforin expression</td>
</tr>
<tr>
<td></td>
<td>KIR family</td>
<td>CD4 T cells</td>
<td>Hypomethylation</td>
<td>Increased KIR expression</td>
</tr>
<tr>
<td></td>
<td>RUNX3</td>
<td>CD4 T cells</td>
<td>Hypermethylation</td>
<td>Dysregulation of ITGAL (CD11a) expression</td>
</tr>
<tr>
<td></td>
<td>MMP9</td>
<td>CD4 T cells</td>
<td>Hypomethylation</td>
<td>Cellular basement membrane breakdown</td>
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<tr>
<td></td>
<td>CD9</td>
<td>CD4 T cells</td>
<td>Hypomethylation</td>
<td>T-cell activation</td>
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<tr>
<td><strong>Histone modification</strong></td>
<td>Histone H4</td>
<td>Monocytes</td>
<td>Increased acetylation</td>
<td>Increased expression of proinflammatory cytokines</td>
</tr>
<tr>
<td><strong>MicroRNA</strong></td>
<td>miR-146a</td>
<td>PBMCs</td>
<td>Underexpression</td>
<td>Type I IFN overproduction</td>
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<tr>
<td></td>
<td>miR-21</td>
<td>CD4 T cells</td>
<td>Overexpression</td>
<td>Downregulation of DNMT1 (indirect) and thus decreased DNA methylation</td>
</tr>
<tr>
<td></td>
<td>miR-148a</td>
<td>CD4 T cells</td>
<td>Overexpression</td>
<td>Downregulation of DNMT1 (direct) and decreased DNA methylation</td>
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<tr>
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<td>miR-125a</td>
<td>PBMCs</td>
<td>Underexpression</td>
<td>Increased KLF expression and thus RANTES overproduction</td>
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<tr>
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<td>miR-126</td>
<td>CD4 T cells</td>
<td>Overexpression</td>
<td>Downregulation of DNMT1 and decreased DNA methylation</td>
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</tbody>
</table>
SLE: players involved in systemic autoimmunity

Environmental triggers
- Virus
- UV
- TLR7/9
- IRF

Antiviral/DNA-damage response
- Apoptosis-related nucleic acids
- Innate response/IFN-I

pDendritic cell
- Cytokines
- IFN-I
- Tissue destruction: kidney, skin, lung

Priming/autoantigen presentation
- MHC
- APC
- TCR
- Antigen
- T cell
- Lymphocyte activation
- Antibody
- B cell
- Cell survival/apoptosis

Apoptotic clearance
- Phagocyte

Immune-complex-dependent response
- Fcγ receptor engagement
- Complement fixation
- IgG immune complex

Autoreactive germinal center reactions
- Plasmablasts
- Plasma cells
- Auto-antibodies: anti-nuclear, anti-cardiolipin etc.
SLE: stages in pathogenesis

Environment

Epigenetics

Triggers

Hormones  Viruses  UV-light  Drugs

Co-morbidites

Symptoms

Disease

Pre-clinical SLE

Clinical SLE

autoantibodies

inflammation

initiating

amplifying

autoimmunity

Normal immunity

Benign Autoimmunity

Pathogenic Autoimmunity

Genetic susceptibility

Organ damage

early / late
SLE: clinical features

- constitutional symptoms (90-95 %)
- mucocutaneous (80-90 %)
- musculoskeletal (80-90 %)
- renal (40-60 %)
- neuropsychiatric (40-60 %)
- ophthalmologic (50-70 %)
- cardiovascular / pulmonary (50-60 %)
- hematologic (20-30 %)
- digestive tract (25-40 %)
- lymphadenopathy, splenomegaly (20-30 %)
Mucocutaneous manifestations

- 80-90%
  - malar rash*
  - discoid lesions*
  - photosensitivity
  - oral/ nasal ulcers
  - Raynaud’s phenomenon
  - alopecia
  - vasculitis
  - urticaria (hives)
Types of cutaneous lupus

**Acute / subacute***
- malar rash (localized – generalized)
- photosensitive
- maculopapular
- annular*
- papulosqamous (psoriasiform)*

**Chronic**
- discoid rash (localized – generalized)
- hypertrophic (verrucous)
- lupus panniculitis (profundus)
- chilblains lupus
- mucosal lupus
facial eruption: malar rash (butterfly erythema)
photosensitive erythema
photosensitive rash
erythematous maculopapular rash
oral ulcers
discoid lupus lesions
subacute cutaneous lupus
diffuse alopecia
Raynaud’s phenomenon
Musculoskeletal disease

- 80-90 %
  - arthralgias / arthritis (pain + stiffness)
    - non-erosive, non-deforming, symmetric
    - small joints of hands, wrists, knees
    - migratory, lasting 24-48 hrs
  - myalgias/ muscle tenderness, weakness
    - myositis: usually proximal
  - avascular bone necrosis
arthritis
Renal disease

(40-60 %)

- glomerulonephritis (lupus nephritis)
- microhematuria
- proteinuria of various levels
- hypertension
- decreased GFR
- renal failure

- tubulointerstitial nephritis
- vascular disease (thrombotic microangiopathy)
2003 ISN/RPS Consensus conference on the classification of lupus nephritis

- **Class I.** Minimal mesangial lupus nephritis (LN)
- **Class II.** Mesangial proliferative LN
- **Class III.** Focal LN (involving < 50% of glomeruli)
  (active, proliferative and/or chronic, sclerosing)
- **Class IV.** Diffuse LN (involving 50% or > of glomeruli)
  (active and/or chronic; segmental or global)
- **Class V.** Membranous LN (global or segmental); (mixed w/III. or IV.)
- **Class VI.** Advanced sclerotic LN (>90% of sclerotic glomeruli)

International Society of Nephrology (*ISN*) /Renal Pathology Society (*RPS*)
Neuropsychiatric manifestations
(40-60 %)

- cognitive dysfunction
- stroke (cerebrovascular disease)
- seizures
- headache
- demyelinating syndrome („lupoid sclerosis”)
- peripheral neuropathies

- psychosis, delirium
- optic neuritis

- cranial neuropathies
- transverse myelitis
- aseptic meningitis
Ophthalmologic manifestations
(50-70 %)

- keratoconjunctivitis sicca
- retinal vasculitis
- episcleritis or scleritis
- anterior uveitis (iritis, iridocyclitis)
Cardiovascular features

(50-60 %)

- pericarditis
- myocarditis
- heart failure, arrhythmias
- valvular disease
  (sterile valvular vegetations: Libman-Sacks endocarditis)
- vasculitis (coronary heart disease)
- premature atherosclerosis
Pulmonary manifestations
(50-60 %)

- pleurisy
- pleural effusion
- pneumonitis
- alveolar hemorrhage
- interstitial lung disease
- pulmonary hypertension
Digestive tract involvement
(25-40 %)

- dysphagia (esophageal hypomotility, reflux)
- abdominal pain
- mesenteric vasculitis / infarction
- protein-losing enteropathy
- pancreatitis
- peritonitis
- exsudative ascites
mesenterial vasculitis (lupus enteritis)
Hematologic abnormalities
(20-30 %)

- Leukopenia (WBC < 4.000/uL)
  - Common
  - Especially lymphopenia (< 1.500/uL)
- Anemia
  - Common (mainly due to chronic inflammation)
  - Autoimmune hemolytic (Coombs +)
- Thrombocytopenia (< 100.000 uL)
  - ITP
  - Anti-CL
- Aplastic anemia: very rare
Coagulopathy

- Hypocoagulable states:
  - anti-platelet antibodies
  - anti-clotting factor antibodies

- Hypercoagulable states (thrombophilia):
  - antiphospholipid antibody syndrome (APS)
  - protein C and S deficiencies

- Thrombotic thrombocytopenic purpura
SLE: diagnostic workup

- no „gold-standard” test/s
- no diagnostic criteria

- dg.: based on clinical judgment!
  - patient’s history, symptoms
  - review of systems
  - physical examination
  - laboratory testing, imaging

- classification criteria
- exclusion of alternative diagnoses
# Classification criteria for SLE

<table>
<thead>
<tr>
<th>Year</th>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>1971</td>
<td>Criteria developed for SLE classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982</td>
<td>Revised classification</td>
<td></td>
<td></td>
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<tr>
<td>1997</td>
<td>Re-revised</td>
<td>83 %</td>
<td>96 %</td>
</tr>
<tr>
<td>2012</td>
<td>SLICC criteria for SLE</td>
<td>97 %</td>
<td>84 %</td>
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</tbody>
</table>

**SLICC**: Systemic Lupus International Collaborating Clinics
## 2012 - SLICC classification criteria

<table>
<thead>
<tr>
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<th>Clinical</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute cutaneous lupus</td>
</tr>
<tr>
<td>2</td>
<td>Chronic cutaneous lupus</td>
</tr>
<tr>
<td>3</td>
<td>Oral or nasal ulcers</td>
</tr>
<tr>
<td>4</td>
<td>Non-scarring alopecia</td>
</tr>
<tr>
<td>5</td>
<td>Arthritis</td>
</tr>
<tr>
<td>6</td>
<td>Serositis</td>
</tr>
<tr>
<td>7</td>
<td>Renal disorder</td>
</tr>
<tr>
<td>8</td>
<td>Neurologic disorder</td>
</tr>
<tr>
<td>9</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>10</td>
<td>Leuko-/lymphopenia</td>
</tr>
<tr>
<td>11</td>
<td>Thrombocytopenia</td>
</tr>
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</table>
### 2012 - SLICC classification criteria

<table>
<thead>
<tr>
<th>Immunologic</th>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>ANA</td>
</tr>
<tr>
<td>2</td>
<td>Anti-DNA</td>
</tr>
<tr>
<td>3</td>
<td>Anti-Sm</td>
</tr>
</tbody>
</table>
| 4 | Anti-phospholipid antibodies  
Lupus anticoagulant  
Anticardiolipin , IgA, IgG or IgM  
Anti-B2-glycoprotein I ,IgA, IgG or IgM |
| 5 | Low complements (C3, C4 or CH 50) |
| 6 | Direct Coombs test (in absence of hemolytic anemia) |
2012 – SLICC classification criteria

(definite) SLE = presence of 4 criteria:

- at least 1 clinical + 1 immunologic
  - OR
- biopsy-proven lupus nephritis
  with ANA or anti-dsDNA antibodies

(Arthritis Rheum, 2012)
- **Probable SLE:** 2-3 of SLICC criteria + at least 1 of major organ involvement:
  * optic neuritis, aseptic meningitis
  * glomerular hematuria
  * pneumonitis, ILD, alveolar hemorrhage
  * verrucous endocarditis
  * mesenterial vasculitis

- **Possible SLE:** 1 of SLICC criteria + at least 2 of organ involvement

- **UCTD:** < 4 of SLICC criteria (only)
<table>
<thead>
<tr>
<th>Antigenic target</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>nucleus/chromatin</td>
<td>ANA</td>
</tr>
<tr>
<td></td>
<td>anti-nucleosome (85 %)</td>
</tr>
<tr>
<td></td>
<td>anti-dsDNS    (80 %)</td>
</tr>
<tr>
<td></td>
<td>anti-histone/s (70 %)</td>
</tr>
<tr>
<td>ribonucleoproteins</td>
<td>anti-ENA</td>
</tr>
<tr>
<td></td>
<td>anti-Sm       (30 %)</td>
</tr>
<tr>
<td></td>
<td>anti-U1RNP    (30 %)</td>
</tr>
<tr>
<td></td>
<td>anti-Ro/SSA   (35 %)</td>
</tr>
<tr>
<td></td>
<td>anti-La /SSB  (15 %)</td>
</tr>
</tbody>
</table>

other targets: *phospholipids, leukocyte / RBC / THR*
*Indirect immunofluorescence test for ANA

*homogeneous pattern; target: chromatin

*speckled: ribonucleoproteins

*peripheral / rim: nuclear targets

DIF: lupus band test (IC at DEJ)
SLE: differential diagnosis

- other autoimmune diseases
  - „rhupus” / RA
  - MCTD
  - Sjögren’s
  - APS
  - UCTD
  - systemic vasculitis
  - adult Still’s disease

- infections

- malignancies
  - NHL
  - MDS
Drug-induced lupus (DIL)

- antiarrhythmics
  - procainamide
  - quinidine
- Antihypertensives
  - hydralazine
  - methyldopa
  - captopril
- Anticonvulsants
  - carbamazepine
  - hydantoin
- anti-infectives: isoniazid
- others: D-penicillamine, sulfasalazine; propylthiouracil
- biologics: TNF-blockers

*10,000-30,000 cases/yr
*F:M = 1:1
*fever, arthritis, rash ~SCLE,
pulmonary involvement,
hepato-splenomegaly,
anemia, leukopenia
*ANA, anti-histone positivity
SLE: disease assessment

Disease Activity Index

- Intermittent disease flares
- Chronically active disease
- Quiescent disease

Disease Damage Index
### Table 7

**SLE Daily Activity Index: Data Collection Sheet**

<table>
<thead>
<tr>
<th>SLEDAI Score</th>
<th>Descriptor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Seizures</td>
<td>Recent onset. Exclude metabolic, infectious or drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Psychosis</td>
<td>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, marked illogical thinking, bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Organic brain syndrome</td>
<td>Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and 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, infection or drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Visual disturbance</td>
<td>Retinal changes of SLE. Include cystoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid or optic neuritis. Exclude hypertensive, infective or drug causes.</td>
</tr>
<tr>
<td>8</td>
<td>Cranial nerve disorder</td>
<td>New onset of sensory or motor neuropathy involving cranial nerves.</td>
</tr>
<tr>
<td>8</td>
<td>Lupus headache</td>
<td>Severe, persistent headache. May be migrainous, but must be nonresponsive to narcotic analgesics.</td>
</tr>
<tr>
<td>8</td>
<td>CVA</td>
<td>New onset of cerebrovascular accident(s). Exclude arteriosclerosis.</td>
</tr>
<tr>
<td>8</td>
<td>Vasculitis</td>
<td>Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, biopsy or angiogram proof of vasculitis.</td>
</tr>
<tr>
<td>4</td>
<td>Arthritis</td>
<td>More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).</td>
</tr>
<tr>
<td>4</td>
<td>Myositis</td>
<td>Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/ aldolase or electromyogram changes or a biopsy showing myositis.</td>
</tr>
<tr>
<td>4</td>
<td>Urinary casts</td>
<td>Hemogranular or red blood cell casts.</td>
</tr>
<tr>
<td>4</td>
<td>Hematuria</td>
<td>&gt;5 red blood cells high power field. Exclude stone, infection or other cause.</td>
</tr>
<tr>
<td>4</td>
<td>Proteinuria</td>
<td>&gt;0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.</td>
</tr>
<tr>
<td>4</td>
<td>Pyuria</td>
<td>&gt;5 white blood cells/high power field. Exclude infection.</td>
</tr>
<tr>
<td>2</td>
<td>New rash</td>
<td>New onset or recurrence of inflammatory type rash.</td>
</tr>
<tr>
<td>2</td>
<td>Alopecia</td>
<td>New onset or recurrence of abnormal, patchy or diffuse loss of hair.</td>
</tr>
<tr>
<td>2</td>
<td>Mucosal ulcers</td>
<td>New onset or recurrence of oral or nasal ulcerations.</td>
</tr>
<tr>
<td>2</td>
<td>Pleurisy</td>
<td>Pleuritic chest pain with pleural rub or effusion, or pleural thickening.</td>
</tr>
<tr>
<td>2</td>
<td>Pericarditis</td>
<td>Pericardial pain with at least 1 of the following: rub, effusion or electrocardiogram or echocardiogram confirmation.</td>
</tr>
<tr>
<td>2</td>
<td>Low complement</td>
<td>Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.</td>
</tr>
<tr>
<td>2</td>
<td>Increased DNA binding</td>
<td>&gt;25% binding by Farr assay or above normal range for testing laboratory.</td>
</tr>
<tr>
<td>1</td>
<td>Fever</td>
<td>&gt;38°C. Exclude infectious cause.</td>
</tr>
<tr>
<td>1</td>
<td>Thrombocytopenia</td>
<td>&lt;100,000 platelets/mm³.</td>
</tr>
<tr>
<td>1</td>
<td>Leukopenia</td>
<td>&lt;3,000 white blood cells/mm³. Exclude drug causes.</td>
</tr>
</tbody>
</table>

**SLEDAI: mild < 5; moderate: 6-12; severe: > 13**

Reprinted, with permission, from Bombardier C[72]
### SLE: chronicity and damage index (SLICC/ACR)

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular</strong></td>
<td></td>
</tr>
<tr>
<td>Any cataract ever</td>
<td>0,1</td>
</tr>
<tr>
<td>Retinal change or optic atrophy</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Neuropsychiatric</strong></td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment/ major psychosis</td>
<td>0,1</td>
</tr>
<tr>
<td>Seizures requiring therapy for 6 months</td>
<td>0,1</td>
</tr>
<tr>
<td>CVA ever (score 2 if &gt;1)</td>
<td>0,1</td>
</tr>
<tr>
<td>Cranial or peripheral neuropathy</td>
<td>0,1</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Estimated GFR &lt;50%</td>
<td>0,1</td>
</tr>
<tr>
<td>Proteinuria &gt;3.5 gm/24 h</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>0,1</td>
</tr>
<tr>
<td>Pulmonary fibrosis and radiograph</td>
<td>0,1</td>
</tr>
<tr>
<td>Shrinking lung (radiograph)</td>
<td>0,1</td>
</tr>
<tr>
<td>Pleural fibrosis (radiograph)</td>
<td>0,1</td>
</tr>
<tr>
<td>Pulmonary infarction (radiograph)</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Angina or coronary artery bypass</td>
<td>0,1</td>
</tr>
<tr>
<td>Myocardial infarction ever (score 2 if &gt; 1)</td>
<td>0,1,2</td>
</tr>
<tr>
<td>Cardiomyopathy (ventricular dysfunction)</td>
<td>0,1</td>
</tr>
<tr>
<td>Valvular disease (murmur &gt;3/6)</td>
<td>0,1</td>
</tr>
<tr>
<td>Pericarditis for 6 months, or pericardiectomy</td>
<td>0,1</td>
</tr>
</tbody>
</table>

### Score by Item

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Claudication for 6 months</td>
<td>0,1</td>
</tr>
<tr>
<td>Minor tissue loss (pulp space)</td>
<td>0,1,2</td>
</tr>
<tr>
<td>Significant tissue loss ever (loss of digit) (score 2 if &gt;1 site)</td>
<td>0,1</td>
</tr>
<tr>
<td>Venous thrombosis, swelling, ulceration, or venous stasis</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Infarction or resection of bowel below duodenum spleen, liver, or gall bladder ever, for cause any (score 2 if &gt;1 site)</td>
<td>0,1,2</td>
</tr>
<tr>
<td>Mesenteric insufficiency</td>
<td>0,1</td>
</tr>
<tr>
<td>Chronic peritonitis</td>
<td>0,1</td>
</tr>
<tr>
<td>Stricture or upper gastrointestinal tract surgery ever</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle atrophy or weakness</td>
<td>0,1</td>
</tr>
<tr>
<td>Deforming or erosive arthritis</td>
<td>0,1</td>
</tr>
<tr>
<td>Osteoporosis with fracture or vertebral collapse</td>
<td>0,1</td>
</tr>
<tr>
<td>Avascular necrosis (score 2 if &gt;1)</td>
<td>0,1,2</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>0,1</td>
</tr>
<tr>
<td>Tendon Rupture</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
</tr>
<tr>
<td>Scarring chronic alopecia</td>
<td>0,1</td>
</tr>
<tr>
<td>Extensive scarring other than scalp and pulp space</td>
<td>0,1</td>
</tr>
<tr>
<td>Skin ulceration (excluding thrombosis) for &gt;6 months</td>
<td>0,1</td>
</tr>
<tr>
<td><strong>Premature gonadal failure</strong></td>
<td>0,1</td>
</tr>
<tr>
<td>Diabetes (regardless of treatment)</td>
<td>0,1</td>
</tr>
<tr>
<td>Malignancy (exclude dysplasia) (score 2 if &gt;1 site)</td>
<td>0,1,2</td>
</tr>
</tbody>
</table>
SLE: principles of treatment

**General:** SLE could be life-threatening!

- rapid diagnosis
- correct assessment of disease extent, activity and severity
- regular clinical monitoring

**Pharmacotherapy:** not curative!

**main goals:** disease activity control, long-term survival

- induction of remission (stop / reverse ongoing organ inflammation)
- prevention or limitation of relapses (irreversible organ damage)
- management of drug-toxicity
SLE: traditional treatment options

- **Approved drugs**
  - corticosteroids
  - hydroxychloroquine
  - low dose aspirin

- **„Off-label” but standard of care**
  - azathioprine
  - cyclophosphamide
  - NSAIDs

- **Immunosuppressives developed for other diseases**
  - methotrexate
  - cyclosporine, tacrolimus (calcineurin inhibitors)
  - mycofenolate mofetil
  - biologics: rituximab
Belimumumab / Benlysta®

- monoclonal anti-sBAFF / BLyS
- the first biologic for SLE
- FDA approval: March, 2011
- the first new drug for SLE in over 50 yrs (!)

**blocking IFNα:** Sifalimumab
Rontalizumab

Abetimus
Blisibimod
Belimumab
Tabalumab
Atacicept
SLE: poor prognostic factors for survival

- renal disease (especially diffuse proliferative LN)
- hypertension
- young age
- poor socioeconomic status
- black race
- presence of antiphospholipid antibodies
- high overall disease activity
SLE: co-morbid conditions

* accelerated atherosclerosis
* osteopenia / osteoporosis
* malignancy (NHL)

SLE: a threefold increased risk of mortality

SLE: leading causes of death

- active lupus (renal, CNS) (21 - 26 %)
- infections (bacterial > viral / fungal) (18 - 25 %)
- cardiovascular disease (~ 25 %)
- late lupus complications (~ 20 %)
SLE: prognosis

1950-1954
Corticosteroids
5-year-survival: 50%

1960-1970s
Cyclophosphamide
Azathioprine
10-year-survival: >60%

1970-1990s
Methotrexate
Organ transplantation
Plasmapheresis
Cyclosporine
10-year-survival: >80%

2000-2010s
Mycophenolate mofetil
Biologics, Rituximab
10-year-survival: ~90%

2011
Belimumab

Improvement in antibiotic,
antihypertensive, and antithrombotic therapies

Adapted from Manzi S, ACR 2012
Thank you for the attention!

May 10: World Lupus Day