Clinical immunology

4th stage

Dr. Thabit Moath

Le No 1
Rheumatoid Arthritis

Rheumatoid Arthritis is a chronic systemic inflammatory disease of undetermined etiology involving primarily the synovial membranes and articular structures of multiple joints. The disease is often progressive and results in pain, stiffness, and swelling of joints. In late stages, deformity and ankylosis develop. Women are affected more than men, with a female: male ratio of 3:1; the disease onset reaches its apex between 35 and 50 years.
Causes

The causes of RA is unknown.

- **Genetic**: Certain HLA-DR4 molecules associated with RA (e.g. HLA-DR beta *0401, 0404, or 0405); in addition, HLA-DR1 (HLA-DR beta *0101) carries this shared epitope and confer risk, particularly in certain southern European areas. (MHCII)

- **Environmental**: for many decades, numerous infection agents have been suggested to induce RA. Among these are Mycoplasma organisms, Epstein Barr virus, rubella virus, cytomegalovirus and herpes virus.

- **Hormonal**: Sex hormones may play a role, as evidenced by the disproportionate number of females with RA, its amelioration (decrease) during pregnancy, its recurrence in the early postpartum period, and its reduced incidence in women using oral contraceptives. Hyperprolactinemia may be a risk factor for RA.
Immunopathogenesis

Rheumatoid Arthritis is a disease result from immunological response to an antigen within the joint. This antigen could be self molecules expressed in the joint or could be foreign (e.g. bacterial or viral) antigen sequestered in joint tissue. The nature of this immunological response and the target antigen remain uncertain.

Unknown antigen stimulates the activation of T lymphocytes that,

in turn activate synovial macrophages. The macrophages secrete the proinflammatory cytokines, TNF-α and IL-1,

which activate osteoclasts and chondrocytes. This "two-pronged attack" results in the destruction of cartilage and bone. The chondrocytes begin to produce high quantities of fibroblast growth factor and (Granulocyte-macrophage colony-stimulating factor (GM-CSF), which completes a harmful cycle that can result in reactivation of the macrophage.
Also, B cells are activated by polyclonal stimulation and produce immunoglobulins, especially rheumatoid factors, that stimulate the activation of complement through immune complex.

Moreover, proinflammatory cytokines, especially TNF-α and IL-1, lead to the increased of proliferation and activation of fibroblast. This result in synovitis with pannus.
**Table:** autoimmune response identified in patients with RA.

<table>
<thead>
<tr>
<th>Autoantigen</th>
<th>Antibodies in RA</th>
<th>T cell response in RA</th>
<th>Specificity for RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>Yes: RF</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Type II collagen and other cartilage antigens</td>
<td>Yes: in 10-20%</td>
<td>Yes: in 10-20%</td>
<td>No</td>
</tr>
<tr>
<td>Citrullinated proteins (CCP)</td>
<td>Yes</td>
<td>Probably</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Figure: Comparison between normal and RA joints.

**Normal Joint**

- Muscle
- Cartilage
- Tendon
- Bone
- Synovium
- Synovial Fluid
- Joint Capsule

**Joint Affected by Rheumatoid Arthritis**

- Bone Loss/Erosion
- Cartilage Loss
- Bone Loss (Generalized)
- Inflamed Synovium
- Swollen Joint Capsule
Symptoms of RA Patients

RA usually affects joints on both sides of the body equally. Wrists, fingers, knees, feet, and ankles are the most commonly affected. The disease often begins slowly, usually with only minor joint pain, stiffness, and fatigue. Joint symptoms may include:

- Morning stiffness, which lasts more than 1 hour, is common. Joints may feel warm, tender, and stiff when not used for an hour.
- Joint pain is often felt on the same joint on both sides of the body.
- Over time, joints may lose their range of motion and may become deformed.
Other symptoms include:

- Chest pain when taking a breath (pleurisy).
- Pericarditis.
- **Eye burning, itching, and discharge.**
- **Nodules** under the skin (usually a sign of more severe disease).
- Burning in the hands and feet.
- Sleep difficulties.
Laboratory diagnosis

- **Synovial fluid analysis**
  - Inflammatory synovial fluid *(WBC count > 2000/µL)* is present with WBC counts generally from 5,000-50,000/µL.
  - Usually, **neutrophil predominance** (60-70%) is observed in the synovial fluid (in contrast with mononuclear cell predominance in the synovium).
  - Because of a transport defect, the glucose levels of pleural, pericardial, and synovial fluids in patients with RA are often low compared to serum glucose levels.

- **Immunological parameters** include autoantibodies (e.g., RF, anti-RF33 (nuclear antigen), anti-CCP, ANA).
  - **Rheumatoid factor (RF)** refers only to the IgM antibody which binds aggregated IgG as antigen. During the first year of illness, rheumatoid factor is more likely to be negative with some individuals converting to seropositive status over time. RF is also seen in other illnesses, for example **Sjögren's syndrome**, Hepatitis C, chronic infections and in approximately 10% of the healthy population, therefore the test is not very specific.
Anti-cyclic Citrullinated peptide (anti-CCP) is the highly sensitivity (90-96%) for RA, can identify RA years before symptoms develop and is the most specific test for Antinuclear antibodies (ANA) are present in approximately 30% of patient with RA. This test is not routinely performed in the early disease.

- C-reactive protein (CRP) for acute active arthritis. (increase)

- Hematological tests
  - Complete blood count (CBC) indicate the presence of anemia in normocytic and normochromic.
  - Thrombocytosis may be present.

- Erythrocyte sedimentation rate (ESR) is elevated in approximately 90% of patient with RA. This test is not routinely performed in the acute setting.
Table 10.5 Some laboratory findings in active rheumatoid arthritis (RA) contrasted with those in active systemic lupus erythematosus (SLE).

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Titre</td>
<td>Positive in 70%</td>
<td>Positive in 30%</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>• Class</td>
<td>IgM</td>
<td>IgG</td>
</tr>
<tr>
<td>• Titre</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>• Proportion of patients positive</td>
<td>40%</td>
<td>95%</td>
</tr>
<tr>
<td>DNA binding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Proportion of patients positive</td>
<td>&lt;10%</td>
<td>70–85%</td>
</tr>
<tr>
<td>C3 + C4 levels</td>
<td>Normal or ↑</td>
<td>↓ or normal</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>↑</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Immunofluorescent examination of a skin biopsy*</td>
<td>–ve</td>
<td>+ve</td>
</tr>
<tr>
<td>Serum IgG levels</td>
<td>Usually normal</td>
<td>Often ↑</td>
</tr>
</tbody>
</table>
B. Pathogenesis of rheumatoid arthritis

- Antigen presentation by synovial cells
- Cytokines
- Complement activation
- Post-capillary venules
  - B cells
  - Arthritogenic peptide
  - Immunoglobulins
  - Rheumatoid factor
  - Immune complexes

- Synovial proliferation
- Synovitis
- Pannus formation
- Bone and joint damage

C. Induction of rheumatoid arthritis

- Unknown antigen
- T cells
- Macrophages
- GM-CSF
- Synovial tissue
- Pannus tissue
- Chondrocytes
- Osteoclasts
- TNF-α
- IL-1
Rheumatoid Arthritis symptoms include:

1. Chest pain when taking a breath (pleurisy).
2. Pericarditis.
3. **Eye burning, itching, and discharge.** Nodules under the skin (usually a sign of more severe disease).
4. **All above**

Rheumatoid arthritis is characterized by the presence of autoantibodies known as:

1. Rheumatoid factors
2. anti-CCP
3. A and B
4. A and B with anti-nuclear antibody
Rheumatoid arthritis RF is an autoantibody, usually of the \[\text{__________}\] that reacts with the Fc portion of IgG

1. IgE class
2. IgM class,
3. IgA class
4. IgD class
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 2
Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is

1. A systemic autoimmune disease

2. characterized by the production of autoantibodies

3. and a diversity of clinical manifestations.

4. It most commonly presents in women during their child-bearing years.

5. the immune system targets intracellular particles that contain both nucleic acids and nucleic acid binding proteins.
Etiology and Pathogenesis

Although the etiology of SLE is unknown, multiple factors are associated with the development of SLE, including

1. genetic (HLA-DR2/DR3),

2. racial,

3. hormonal, immune abnormalities

4. and environmental factors (ultraviolet light, viral infection involving molecular mimicry between organism and self for example anti-Sm autoantibody react with p24 gag protein of retroviruses and that anti- Ro recognizes a nucleocapsid protein on vesicular stomatitis virus).
One proposed mechanism for the development of autoantibodies involves a defect in apoptosis or clearance of apoptotic cells, leading to a disturbance in immune tolerance.

The redistribution of cellular antigens during apoptosis leads to a display of cytoplasmic and nuclear antigens on the cell surface, enhancing immune reactivity to antigens, which are normally protected intracellularly. Activation of antigen-presenting cells by IFN-α might promote presentation of autoantigens to self-reactive T cells.

Immune complexes form in the microvasculature, leading to complement activation and inflammation.

Antibody–antigen complexes deposit on the basement membranes of skin and kidneys. In active SLE, this process has been confirmed based on the presence of complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins at these sites.
INATE SUSCEPTIBILITY
- HLA type (DR3/2)
- Immunoregulatory genes (multiple)
- Complement levels
- Hormonal levels

ENVIRONMENTAL STIMULI
- UV exposure
- Microbial response
- Drugs

AUTOIMMUNE PROLIFERATION
- Hyperactive B-cell/T-cell activation
- High ratio of CD4:CD8 T-cells
- Defective immune complex clearance
- Impaired tolerance

AUTOANTIBODY PRODUCTION
- Apoptosis & self exposure
- Self-recognition
- Foreign-Ab cross reaction
Double stranded DNA
Systematic lupus erythematosus
(chronic active hepatitis)

Histones

Single-stranded DNA
Non-specific
i.e. elderly and many
rheumatic conditions

Nucleolus
Scleroderma

Non-histone nuclear proteins
e.g. Sm — systemic lupus erythematosus
RNP — mixed connective tissue disease
Ro — vasculitis/SLE/Sjögren's syndrome
La — Sjögren's syndrome
Clinical Features

Systemic lupus erythematosus is a multisystem disease and can affect virtually all organs and system; whilst some manifestations are common, others are rare. Therefore, joint, skin and blood are affected in 80-100% of patients, kidneys, CNS and cardiopulmonary system in over 50%; while thrombosis, a typical lupus manifestation associated with possession of the anticardiolipin antibody, is present in 10% of patients.

Systemic manifestations including fatigue, malaise, fever, anorexia, nausea and weight loss, are present in the great majority of patients.

The symptoms difference according to the infected organ and including arthritis, arthralgia, malar rash, an erythematous rash over the nasal bridge, photosensitivity, discoid lesions, headache, migraine, nephrotic syndrome, pleuritis and pericarditis.
<table>
<thead>
<tr>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Malar rash</td>
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<tr>
<td>Discoid rash</td>
</tr>
<tr>
<td>Photosensitivity</td>
</tr>
<tr>
<td>Oral ulcers</td>
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<tr>
<td>Non-erosive arthritis</td>
</tr>
<tr>
<td>Serositis (pleuritis/pericarditis)</td>
</tr>
<tr>
<td>Renal disease (persistent proteinuria/urinary casts)</td>
</tr>
<tr>
<td>Neurological disorder (seizures/psychosis)</td>
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<tr>
<td>Haemolytic anaemia/leucopenia/lymphopenia/thrombocytopenia</td>
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<tr>
<td>Antinuclear antibody</td>
</tr>
<tr>
<td>Antibodies to dsDNA/antibodies to extractable nuclear antigens/antiphospholipid antibodies</td>
</tr>
</tbody>
</table>

*To establish a diagnosis of SLE a patient must have four or more of these criteria.*
General laboratory findings

The most frequent laboratory alteration that is identified is normochromic normocytic anemia of chronic disorders. Occasionally a Coombs-positive hemolytic anemia is observed. Leukopenia (probably autoantibody mediated), especially lymphopenia, and thrombocytopenia are frequent. The erythrocyte sedimentation rate is typically elevated, while C-reactive protein tends to be normal. Urinalysis can show haematuria, proteinuria and renal casts in the presence of glomerulonephritis.
Immunological laboratory findings

All patients in whom SLE is suspected should be tested for antinuclear antibodies, including those to dsDNA and extractable nuclear antigens (ENA), and for antiphospholipid antibodies, as well as having their serum level of IgG and complement components, C3 and C4 measured.

Antihistone antibodies are also present in patients with drug-induced SLE, most frequently associated with hydralazine and procainamide therapies.
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</tr>
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</tr>
<tr>
<td><strong>DNA binding</strong></td>
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</tr>
<tr>
<td><strong>C3 + C4 levels</strong></td>
</tr>
<tr>
<td><strong>C-reactive protein</strong></td>
</tr>
<tr>
<td><strong>Immunofluorescent examination of a skin biopsy</strong></td>
</tr>
<tr>
<td><strong>Serum IgG levels</strong></td>
</tr>
</tbody>
</table>
The sero-immunological hallmark of SLE is antinuclear antibodies (ANA), in the absence of ANA, the diagnosis of SLE is put into question, even though some 5% of patients may have an ANA-negative serology. ANA is currently detected by an indirect immunofluorescence technique, where diluted patients serum is applied to frozen tissue, especially liver, of rodent origin and cell lines of human origin, such as the HEp2 cell line derived from a laryngeal tumor, in which nuclei are prominent, are used as substrate to detect ANA. If the patient is ANA positive, the autoantibody will bind to nuclei. To reveal this binding, a second antibody tagged with fluorescent label is add. This second antibody will bind and ANA will then be seen by placing the preparation under a fluorescence microscope. Four patterns of fluorescence can be seen indicating different types of antinuclear antibodies.
1. Rim pattern (150x magnif; anti-DNA)
2. Homogenous pattern (435x enlarged; anti-DNA)
3. Nucleolar pattern (e.g. fibrillarin)
4. Coarse-speckled pattern (U1RNP/Sm)
5. Fine-speckled pattern (Ro/La)
6. Anti-centromere antibody pattern
<table>
<thead>
<tr>
<th>Pattern</th>
<th>Antigen</th>
<th>Disease association(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
<td>Double-stranded DNA</td>
<td>SLE</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>DNA-histone complexes</td>
<td>SLE and other connective tissue diseases</td>
</tr>
<tr>
<td>Speckled</td>
<td>Non-DNA nuclear antigens</td>
<td>SLE and other connective tissue diseases</td>
</tr>
<tr>
<td></td>
<td>Sm</td>
<td>SLE</td>
</tr>
<tr>
<td></td>
<td>ribonucleoprotein</td>
<td>Mixed connective tissue disease, SLE, scleroderma, etc.</td>
</tr>
<tr>
<td></td>
<td>SS-A, SS-B</td>
<td>Sjögren’s disease</td>
</tr>
<tr>
<td>Nucleolar</td>
<td>Nucleolus-specific RNA</td>
<td>Scleroderma</td>
</tr>
</tbody>
</table>

Double stranded DNA
Systemic lupus erythematosus (chronic active hepatitis)

Single-stranded DNA
Non-specific i.e. elderly and many rheumatic conditions

Non-histone nuclear proteins
e.g. Sm — systemic lupus erythematosus
RNP — mixed connective tissue disease
Ro — vasculitis/SLE/Sjögren’s syndrome
La — Sjögren’s syndrome
ANA is a very sensitive test for SLE, being present in virtually all patients and frequently at high titers; its disease specificity is relatively low since it is frequently found in other rheumatic diseases, as well as in autoimmune liver disease, during viral infections and, occasionally, at low titers, in normal subjects.
DNA antibodies are the most important in SLE. They can react with single-stranded DNA (ssDNA) or with double-stranded DNA (dsDNA). Although anti-ssDNA may be found in many diseases besides SLE, anti-dsDNA autoantibodies are found almost exclusively in SLE (70% of the patients). While the disease specificity of dsDNA autoantibodies is high, that of ANA is low.
Anti-dsDNA autoantibodies are usually detected by very analytically sensitive technique, such as radioimmunoassay (RIA) or enzyme linked immunosorbent assay (ELISA). They can also be detected by immunofluorescence staining of an organelle called a kinotoplast in the flagellate *Crithidia luciliae*, which contains dsDNA.
In a patient with lupus nephritis, a kidney biopsy is frequently obtained for diagnostic reasons the glomeruli of such biotic renal material contain antigen-antibody complexes. By applying a fluorescent antibody directed against human antibody (similar to that used in the second step of ANA detection) to frozen section of the kidney biopsy. This one step technique is known as direct immunofluorescence.
Extractable nuclear antigens (ENA) include Sm (Smith), RNP (ribonucleoprotein), Ro (Robert) also called SS-A (Sjogrens syndrome antigen A) and anti-La (Lane) or SS-B (Sjogrens syndrome antigen B).

Anti-ENA antibodies are include anti-Sm found almost exclusively in SLE, and anti-RNP more typically associated with mixed connective tissue disease than with SLE, anti-Ro and anti-L are found in Sjogrens syndrome. Other Anti-ENA antibodies are anti-Jo-1, anti Scl-70 and anticentromere, which are associated mainly with polmyositis, systemic sclerosis and CREST syndrome respectively. Anti-ENA antibodies are normally detected by immunodiffusion or ELISA technique.

The lupus anticoagulant causes a prolonged clotting time in vitro but thrombosis in vivo. It is often found in associated with other autoantibodies to phospholipids, such as anticardiolipin antibodies and false positive tests for syphilis.
Assessment of the complement profile is of importance in management. Serial determinations of CH$_{50}$, a functional assay measuring complement hemolytic activity, and of the individual factors C3 and C4, inform on how much immune complexes are consuming complement.

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</tr>
<tr>
<td>* Titre*</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
</tr>
<tr>
<td>* Class*</td>
</tr>
<tr>
<td>* Titre*</td>
</tr>
<tr>
<td>* Proportion of patients positive DNA binding*</td>
</tr>
<tr>
<td>Proportion of patients positive</td>
</tr>
<tr>
<td>C3 + C4 levels</td>
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<td>Immunofluorescent examination of a skin biopsy*</td>
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<td>Serum IgG levels</td>
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<td></td>
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<tr>
<td>Immunological test</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>dsDNA binding</td>
</tr>
<tr>
<td>Antinuclear bodies (high titre; IgG class)</td>
</tr>
<tr>
<td>Raised serum IgG level</td>
</tr>
<tr>
<td>Low serum complement C3/C4 levels</td>
</tr>
<tr>
<td>Platelet antibodies</td>
</tr>
<tr>
<td>Cryoglobulinaemia</td>
</tr>
<tr>
<td>Antibodies to ENA:</td>
</tr>
<tr>
<td>Sm</td>
</tr>
<tr>
<td>RNP</td>
</tr>
<tr>
<td>Ro</td>
</tr>
<tr>
<td>La</td>
</tr>
<tr>
<td>Antibodies to phospholipids</td>
</tr>
<tr>
<td>Rheumatoid factor (low titre)</td>
</tr>
<tr>
<td>Skin biopsy IgG, C3 and C4 deposits in normal skin</td>
</tr>
</tbody>
</table>

* Figures show percentage of patients with positive tests.

ESR, erythrocyte sedimentation rate; ENA, extractable nuclear antigens; RNP, ribonucleoprotein.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 3
**Ankylosing spondylitis**

1. The term spondyloarthritis (SpA) (otherwise known as spondyloarthropathy) encompasses a heterogeneous group of inflammatory diseases

2. characterized by spinal and peripheral joint oligo arthritis (one third of the patients), and sacroiliac joints.

3. inflammation of the attachments of ligaments and tendons to bones (enthesitis) and, at times,

4. mucocutaneous, ocular manifestations (, iritis is the most troublesome: it tends to be unilateral and accompanied by photophobia pain)

5. and/or cardiac manifestations.

6. These disorders show familial aggregation and are typically associated with genes of the major histocompatibility complex (MHC), particularly human leukocyte antigen (HLA)-B27 (90% positive)
7. It is **progressive disease**

8. in which **restriction of movement**

9. is associated with **intervertebral ossification of the ligaments**.

10. **Men, usually below the age of 40, man develop the disease three times more frequently than women.**

11. The etiology of the disease is unknown, but persistence of specific antigens of the infecting organisms has been demonstrated in these patients. This has led to suggestion that **AS is also triggered by infection** (possibly in the gastrointestinal tract) in susceptible HLA-B*27- positive individuals. *(Inflammation of the colon and ileum is frequent but usually asymptomatic.)*

12. **The onset of AS tends to be mild lumbar pain; this persists over 3 months and sudden morning stiffness relieved by exercise**
Criteria of AS Classification

**Inflammatory Spinal Pain**: History or present symptoms of spinal pain in back, dorsal or cervical region with at least 4 of the following:

- **A.** Onset at age < 45 years.
- **B.** Insidious onset.
- **C.** Improved by exercise.
- **D.** Associated with morning stiffness.
- **E.** at least for 3 months duration.

**Synovitis**: Asymmetric or Predominantly in the lower limbs. and one of the followings:

- Positive family history/Psoriasis/Inflammatory bowel disease./Alternating buttock pain./Enthesopathy/Acute diarrhea.
- Urethritis/Sacro iliatis.
Etiology of AS

Inflammation occurs and persists in different organs and joints in Ankylosing Spondylitis. Each individual tends to have their own unique pattern of presentation and activity of the illness. The initial inflammation may be a result of an activation of body's immune system, perhaps

1. by a **preceeding bacterial infection** or a combination of infectious microbes.

2. Once activated, the body's **immune system becomes unable to turn itself off**, even though the initial bacterial infection may have long subsided.

3. Chronic tissue inflammation resulting from the **continued activation of the body's own immune system in** the absence of active infection is the hallmark of an inflammatory autoimmune disease.

4. The tendency to develop Ankylosing Spondylitis is believed to **be genetically inherited**, and the majority (nearly 90%) of patients with Ankylosing Spondylitis are born with the HLA-B27 gene.

5. Some additional factor(s), **perhaps environmental**, are necessary for the disease to appear or become expressed.
Pathogenesis

Genetic Predisposing Factor (HLA-B 27) with CD8 T cells (TNF α) and IL-1 are also implicated in AS.

Anti-neutrophil cytoplasmic antibodies (ANCA) are associated with AS. AS arises from a cross-reaction between HLA-B27 and antigens of the Klebsiella bacterial strain.
Clinical Features

1. Chronic pain and stiffness in the lower part of the spine.
2. An inflammation of the eye (iridocyclitis and uveitis), causing redness, eye pain, vision loss, floaters and photophobia.
3. Generalized fatigue and sometimes nausea
4. Less commonly aortitis, apical lung fibrosis and ectasia of the sacral nerve root sheaths may occur.
5. Other forms of spondyloarthropathies are associated with ulcerative colitis, Crohn's disease, psoriasis, and Reiter's syndrome (reactive arthritis).
The diagnosis of Ankylosing Spondylitis is based on:

- Evaluating the patient's symptoms
- A physical examination
- X-ray findings
- Blood tests
The examination can demonstrate signs of:

1. Symptoms include pain and morning stiffness of the spine and sacral areas with or without accompanying inflammation in other joints, tendons, and organs.

2. Inflammation and decreased range of motion of joints. This can be particularly apparent in the spine.

3. The Schober’s test is a useful clinical measure of flexion of the lumbar spine performed during examination. Flexibility of the low back and/or neck can be decreased.

4. There may be tenderness of the sacroiliac joints of the upper buttocks.

5. The expansion of the chest with full breathing can be limited because of rigidity of the chest wall.
Laboratory findings Blood & Other Tests

1. The presence of the blood test *genetic marker, the HLA-B27 gene.*

2. *Increase in the blood concentration of CRP & ESR is a nonspecific marker* for inflammation throughout the body and is often elevated in conditions such as Ankylosing Spondylitis.

3. *Urine Analysis is* often done to look for accompanying abnormalities of the kidney.
Differential Diagnosis of AS

- **kidney conditions that may produce back pain** that mimics Ankylosing Spondylitis
- Patients are also simultaneously evaluated for symptoms and signs of other related spondyloarthropathies, such as **Psoriasis**.
- **Venereal disease**.
- **Dysentery** *(reactive arthritis or Reiter's disease)*.
- **Inflammatory bowel disease** *(ulcerative colitis or Crohn's disease)*.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 4
Psoriatic Arthritis

Skin involvement exhibits four clinical patterns.

1. The most common type is psoriasis vulgaris.
2. Nearly as common is guttate psoriasis. The most severe type is the erythrodermic variety.
3. Finally, pustular psoriasis is the type most closely associated with HLA-B27.
Usually the disease appears coincident
1. with or after the onset of skin manifestations,
2. although approximately 15–20% of patients will have pre-existent arthritis. The joint disease likewise occurs in different subtypes, as defined by the Moll and Wright classification, including
   a). oligoarticular, asymmetric, polyarticular, symmetric, distal interphalangeal (DIP)-predominant, spondylitis (sacroiliitis), arthritis mutilans, inflammation of DIP joints (often with nail involvement (~ 80%)), dactylitis: “sausage digits,” and enthesitis. Extra-articular features include nail pitting (which correlates best with DIP involvement) and uveitis (which occurs in some series as high as 33% but in most far less). Radiographically, large eccentric erosions are encountered.
(MCP) and proximal interphalangeal (PIP) joints than the lower extremities, and is more likely to have a chronic course. The symptoms of peripheral arthritis tend to coincide with activity of the bowel disease in UC but not in Crohn’s disease. Total colectomy is associated with remission of arthritis in half of patients. In contrast, axial involvement may precede the development of IBD, has no gender predilection, and resembles the development of AS. The axial symptoms do not parallel activity of bowel disease. In addition to spondylitis, an isolated sacroiliitis occurs that is often asymmetric and not associated with HLA-B27. Mucocutaneous complications of IBD include erythema nodosum, which occurs in fewer than 10% of those with Crohn’s disease and is rare in UC; pyoderma gangrenosum, seen in slightly over 1% of those with Crohn’s disease and rarely occurring in those with UC; and, rarely, erythema multiforme. Painful aphthous ulcers occur in about 8% of those with UC and are rare in Crohn’s disease.
The uveitis with IBD that is bilateral, posterior, insidious in onset, and/or chronic in duration contrasts with the uveitis associated with other types of SpA, which is predominantly anterior, unilateral, sudden in onset, and limited in duration. Only 46% of patients with uveitis associated with IBD are HLA-B27-positive, as opposed to 89% of the patients with SpA. Episcleritis, scleritis, and glaucoma are more common among patients with IBD than in those with SpA.
Patterns of psoriatic arthritis, showing (A) rheumatoid-like distribution; (B) sausage digits; (C) distal interphalangeal involvement; and (D) psoriatic arthritis mutilans.
Psoriatic Arthritis (PsA) is a chronic and inflammatory arthritis in association with skin psoriasis, characterized by osteolysis and bony proliferation. PsA is classified as one of the subtypes of spondyloarthropathies. Males and females are equally affected. PsA can range from mild nondestructive disease to a severely rapid and destructive arthropathy.

Clinical manifestations include skin and nail psoriasis, dactylitis, enthesitis, osteoperiostitis, large joint oligoarthritis, arthritis mutilans, sacroiliitis, spondylitis and distal interphalangeal arthritis.
sacroiliitis

spondylitis

distal interphalangeal arthritis

nail psoriasis

enthesitis

osteoperiostitis,

arthritis mutilans
Comorbidities in PsA Patients

- Ocular inflammation (Iritis/Uveitis/Episcleritis).
- Irritable bowel disease (IBD).
- Metabolic Syndrome (Hyperlipidemia, Hypertension, Insulin resistant, Diabetes, Obesity) lead to Higher risk of Cardiovascular disease (CVD).
- Psychosocial burden, Reactive depression, Higher suicidal ideation and Alcoholism.

Two percent of patients with psoriasis develop psoriatic arthropathy; this may affect the peripheral joints or the spine. The psoriasis generally precedes the arthritis by many years; in rare cases where the arthritis comes first, diagnosis may be difficult. A family history of psoriasis is a helpful diagnostic clue and the characteristic nail changes of psoriasis are present in 80% of patients with psoriatic arthritis. Dactylitis – inflammation of an entire digit to look like a sausage – is a distinctive feature. Usually rheumatoid factor (RF) negative and ACPA negative. Radiographic damage can be noted in up to 47% of patients at a median interval of two years despite clinical improvement with standard DMARD therapy.
Treatment is similar to that for RA, including the use of anti-TNF drugs. The prognosis is usually good, although severe joint destruction can occur.
Clinical immunology

4th stage
Dr. Thabit Moath
Le No 5
Sjögren's Syndrome

Sjögren’s syndrome (SS) is a chronic systemic autoimmune disease characterized by lachrymal and salivary gland dysfunction. It was named after the Swedish ophthalmologist Henrik Sjögren after he reported 19 cases of keratoconjunctivitis in 1933.1 The hallmark feature of SS is deficient tear and saliva production due to lymphocytic infiltration of the salivary and lachrymal glands leading to xerostomia (dry mouth) and xerophthalmia (dry eyes). In addition, SS can involve any organ system and present with a wide spectrum of clinical features. The autoimmune process seems to primarily affect the lining epithelium of various organs; in fact some experts propose the term “autoimmune epithelitis” to be used instead of SS.

- Most individuals with Sjögren's syndrome present with sicca symptoms, such as Conjunctivitis Sicca (dry eyes), xerostomia (dry mouth), & parotid gland enlargement.

- In addition, numerous extra glandular features may develop, such as arthralgia, arthritis, Raynaud's Phenomenon, Myalgia, Pulmonary disease, Gastrointestinal disease, leukopenia, anemia, lymphadenopathy, neuropathy, vasculitis, renal tubular acidosis, and Lymphoma.
**Epidemiology**

Sjögren’s syndrome predominantly affects females (female : male ratio 9:1) in their fourth and fifth decades of life. However, symptoms can be present for much longer time and there is usually a 5- to 10-year delay in the diagnosis of SS.
**Environmental factors**

The inciting event in the pathogenesis of SS is not known, and it may not be a single event. The strong predominance of females suggests

1. **gender-specific** predisposing factors.

2. Although **sex hormones** are obvious targets, there is no conclusive proof yet that the difference in the pathogenesis between males and females is due to sex hormones alone. Estrogens are considered contributors to autoimmunity, whereas androgens are thought to be protective. But since the **peak age of onset in SS occurs around menopause**, characterized by a **decrease in estrogens**, the increased risk may be due to a change in the androgen–estrogen ratio rather than absolute levels of estrogens.

3. **Viral infections** have also been proposed as inciting events. This theory is strongly supported by the fact that chronic inflammation of the salivary glands has been observed with **chronic hepatitis C, HTLV-1, and human immunodeficiency virus infections**.
Pathophysiology

Sjögren's syndrome can occur as a primary disease of exocrine gland dysfunction or as a secondary in association with several other autoimmune diseases (e.g. SLE, RA, Scleroderma c Sclerosis, Cryoglobulinemia).

- These primary and secondary types occur with similar frequency, but the sicca complex seems to cause more severe symptoms in the primary form.
**Immunopathogenesis**

The pathogenesis of SS is still largely unknown. In a genetically predisposed individual, various environmental factors, such as viral infections, may lead to epithelial cell activation and a protracted inflammatory response with features of autoimmunity. Autoreactive lymphocytes and autoantibodies are considered important in this process, although the pathogenic role of any particular autoantibody is still undefined.
Etiology of Sjögren's Syndrome

- Immunological Factors.
- Neurological Factors.
- Apoptotic Mechanisms.
Immune Mechanism

• Cell-mediated immune mechanisms likely play a central role in the inflammation that leads to tissue damage in SS.

• CD4 T helper cells predominate in the focal lymphocytic infiltrates that characterize involved salivary and lacrimal glands.

• Expression of certain HLA molecules on the epithelial cells enhance hypergammaglobulinemia with the elevation of RF, Ro & La autoantibodies.

Neuroendocrine Mechanism

A. Proinflammatory cytokines released by epithelial cells and lymphocytes may impair neural release of acetylcholine.

B. In addition, antibodies to acetylcholine (muscarinic) receptors may interfere with the neural stimulation of local glandular secretion, perhaps by interfering with aquaporin.

C. Moreover, a recent study reports that M3 muscarinic receptor antibodies may cause autonomic dysfunction in patients with Sjögren syndrome.
Apoptotic Mechanism

A defect in Fas-mediated apoptosis, which is necessary for down-regulation of the immune response, can result in a chronic inflammatory destruction of the salivary gland, resembling Sjögren’s Syndrome.
Chronic fatigue is a prominent presenting feature of Sjögren syndrome.

**Autonomic and peripheral nervous system involvement** is often under recognized.

Mimics of Sjögren’s syndrome include IgG₄-related disease (Mikulicz’s disease), hepatitis C infection, sarcoidosis, and HTLV infection.

Presence of joint erosions and CCP antibody is indicative of secondary Sjögren syndrome due to rheumatoid arthritis.

Avoid prolonged use of topical ophthalmic NSAID and steroid preparation due to increased risk of complications.

Sudden normalization of previously elevated rheumatoid factor should prompt evaluation for development of lymphoma.

Identify and treat oral candidiasis. Sjögren syndrome patients are at a **high risk** for oral candidiasis, which can present as oral erythema and/or pain.

**Pediatric primary** Sjögren syndrome is rare and presents with variable, atypical features most commonly recurrent tender parotid gland swelling.
Clinical Features:

- Xerostomia
- Conjunctivitis sicca (ocular signs).
- **Skin**, nose, and **vaginal dryness**, and may affect other **organs** of the body,
- including the **kidneys**, blood vessels, lungs, liver, pancreas, and brain.
- Patients with secondary SS also have signs and symptoms of the associated rheumatic disorder.
Classification criteria

1. Ocular symptoms
   - Dry eyes for more than 3 months
   - Foreign-body sensation
   - Use of tear substitutes more than 3 times per day

2. Oral symptoms (Xerostomia)
   - Feeling of dry mouth
   - Recurrently swollen salivary glands
   - Frequent use of liquids to aid swallowing
Ocular signs (Conjunctivitis Sicca)

- Schirmer test performed without anesthesia (<5 mm in 5 min)
- Positive vital dye staining results

1. Oral signs
   - Abnormal salivary scintigraphy findings
   - Abnormal parotid sialography findings
   - Abnormal sialometry findings (unstimulated salivary flow <1.5 mL in 15 minutes)

2. Positive anti–SSA or anti–SSB antibody results

3. Positive minor salivary gland biopsy findings Diagnosis
I. **Laboratory Studies**

1. Complete blood count (CBC) [showed low platelets & WBCs, ESR is elevated in 80%] of patients.

2. Chemistry Tests:
   - Creatinine clearance may be diminished in up to 50% of patients.
   - A high total protein level or a low albumin level should prompt the clinician to perform serum protein electrophoresis.
   - A high alkaline phosphatase level should prompt consideration for primary biliary cirrhosis.
   - With elevated transaminase levels, consider the possibility of chronic active hepatitis, which can be associated with sicca symptoms, or hepatitis C, which can cause mild salivary gland enlargement. However, mild (<2-fold) increases in transaminase levels have been observed in 22% of patients with Sjögren syndrome.
• Consider evaluating patients with a low bicarbonate level for type I (distal) renal tubular acidosis. Less commonly, patients can also develop proximal renal tubular acidosis with Fanconi syndrome.

• Hypokalemia, occasionally severe enough to lead to periodic paralysis, can be observed in patients with type I renal tubular acidosis but can also be observed in patients who have Sjögren syndrome without renal tubular acidosis.
• **Schirmer's test**

• **Serum protein electrophoresis**

  • Patients with Sjögren syndrome often have a polyclonal **gammopathy**.
  
  • Loss of a previously detected polyclonal gammopathy can be observed in some patients with Sjögren syndrome who develop lymphoma.

  • Development of a monoclonal gammopathy can also signal the development of a lymphoma.
- **Autoantibodies**
  - Anti-SS-A and anti-SS-B are present in most cases of primary-type Sjögren's syndrome,
  - while antislavery duct antibodies are present in most cases of the secondary type.
  - Other autoantibodies, such as anti-nuclear antibodies and rheumatoid factor, are frequently present in patients with both primary and secondary SS. Although they lack specificity, they are markers of a systemic autoimmune response and thus can help distinguish SS from other causes of salivary or lachrymal gland dysfunction.
  - In recent years, research has focused on identifying antibodies more specific for SS, such as anti-a-fodrin and anti-muscarinic acetylcholine receptor antibodies, but the results have been controversial. The major stimulus for saliva production is the binding of acetylcholine to muscarinic acetylcholine receptors. The hypothesis that oral and ocular drynessness could result from antibodies antagonizing the muscarinic acetylcholine receptor-3 is intriguing.
  - Antinuclear antibodies of the speckled and homogeneous type are present in most cases of primary Sjögren's syndrome.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 6
Behcet's disease
Behcet's disease is a rare, chronic, lifelong disorder that involves inflammation of blood vessels throughout the body. It is a form of vasculitis that can lead to ulceration and other lesions slightly affecting more men than women characterized by a triad of symptoms, including aphthous ulceration of the oral mucous membranes and genitalia and uveitis.

Rare manifestations include oligoarthritis of the lower extremities, vasculitis of the pulmonary vessels, cerebrovascular symptoms.
The etiology of the Behcet's disease is unknown. It is believed to be partly genetic, an association with HLA-B51 has been found.
Figure: Pathogenicity of Behcet's disease
Risk factors

- **Age.** Behcet's disease most commonly affects men and women in their 20s, 30s and 40s, though children and older adults also can develop the condition. *When the condition occurs at an earlier age, it tends to be more severe.*

- **Geography.** Although the disease occurs worldwide, people from countries in the Middle East and Asia, including Turkey, Iran, Iraq, Japan and China, are more likely to develop Behcet’s.
Sex. While Behcet's disease occurs in both men and women, the disease is usually more severe in men.

Genes. Having certain genes HLA-B51 is associated with a higher risk of developing Behcet's.
Clinical features

- **Mouth:** Painful mouth sores, identical to canker sores, are the most common sign of Behcet's disease. Sores begin as raised, round lesions in the mouth that quickly turn into painful ulcers. The sores heal usually in seven to 21 days, though they do recur.

- **Skin:** Skin lesions may occur in people with Behcet's disease. Skin problems can vary. Some people may develop acne-like sores on their bodies. Others may develop nodules on the lower legs.

- **Genitals:** People with Behcet's disease may develop sores on their genitals. The sores most commonly occur on the scrotum or the vulva.

- **Eyes:** Behcet's disease may cause inflammation in the eye — a condition called uveitis. In people with Behcet's disease, uveitis causes redness, pain and blurred vision in one or both eyes.

- **Joints:** Joint swelling and pain most commonly affect the knee in people with Behcet's disease.

- **Vascular system:** Inflammation in veins and large arteries may occur in Behcet's disease, causing redness, pain and swelling in the arms or legs when a blood clot results.

- **Digestive system:** Behcet's disease may cause abdominal pain, diarrhea or bleeding.

- **Brain:** Inflammation in the brain and nervous system that leads to headache, fever, disorientation, poor balance and stroke.
Diagnosis

There is no diagnostic test and the diagnosis is entirely clinical. Laboratory findings are **nonspecific** and reflect the inflammatory state,

1. C-reactive protein levels,

2. erythrocyte sedimentation rate (ESR),

3. leukocyte count,

4. complement components,

5. and acute-phase reactants may all be elevated during an acute attack. Internationally accepted diagnosis criteria have been published recently.
International Clinical Criteria for Behcet's Disease

An international group of physicians has established a set of guidelines to aid in the classification of Behcet's patients. The International Clinical Criteria for Behcet's Disease classification states patients must present with:

- Recurrent oral ulcerations (apthous or herpetiform) at least three times in one year.
- Additionally, patients must present any two of the following:
  - Recurrent genital ulcerations.
  - Eye lesions (uveitis or retinal vasculitis) observed by an ophthalmologist. Skin lesions (a variety of rashes or acne-like sores) may be caused by Behcet's disease.
  - Positive pathergy test, your doctor inserts a sterile needle into your skin and then examines the area two days later. If the pathergy test is positive, a small red bump forms under your skin where the needle was inserted. This
Treatment

In the meantime, no specific treatment is available, although corticosteroids may control symptoms and azathioprine and adalimumab (a humanized antibody to TNF-α) have been shown to reduce progression of visual loss. In severe cases, ciclosporin, tacrolimus and infliximab may be effective. Thalidomide may be useful in refractory orogenital ulceration.
Clinical Immunology 4ed stage Dr. Thabit moath Le No 7
Gluten Sensitive Enteropathy (GSE) or Celiac Disease

Celiac disease (CD), an immune-mediated mucosal disorder primarily affecting the small intestine in genetically susceptible individuals, is triggered by the ingestion of dietary gluten. Gluten is the alcohol-soluble protein component of the cereals wheat, rye and barley.

It is composed of 2 major protein fractions: glutenin and gliadin; most of the toxic activity exerted by gluten in CD is due to gliadin.

It is also known as celiac sprue, gluten-sensitive enteropathy, non-tropical sprue, characterized by inflammation leading to injury to the mucosal lining of the small intestine, including villous atrophy with crypt hyperplasia, intraepithelial lymphocytosis, and subsequent nutrient malabsorption.
Normal

Tall slender villi

Goblet cell

Intraepithelial lymphocytes

Lamina propria

Scattered lymphocytes and plasma cells

Muscularis mucosa

Subtotal villous atrophy

Loss of villi; flattened epithelium

Increased numbers of intraepithelial lymphocytes

Inflammatory cell infiltrate (plasma cells, lymphocytes and mast cells)
The disorder is a multifactorial condition, originating from the interplay of genetic and environmental factors. The necessary environmental trigger is gluten, timing of gluten introduction into the diet could play a role in pathogenesis, since initial exposure to wheat, barley, or rye in the first 3 months of life or after the 7th months proved to be related to an increased risk of CD. Breast-feeding could have a protective effect, since introduction of

While, the genetic predisposition has been identified in the major histocompatibility complex region on chromosome 6p21, with over 90% of CD patients expressing human leukocyte antigens HLA DQ2 and the remaining celiac patients express DQ8. Some infectious agents could increase the risk of celiac disease, like repeated infection with rotavirus, the most common cause of childhood gastroenteritis, represent an independent risk factor for celiac disease in genetically susceptible individuals.
Some drugs can have a role in enhancing a person’s susceptibility to gluten, a course of interferon alfa could activate celiac disease in predisposed people.

- Abnormal small intestine lining from injury. Injury is the result of gluten-induced inflammation. It is an autoimmune reaction with common triggers. The risk is genetically inherited. Malabsorption occurs as a result.

Genetically
environmental factors
Some infectious agents
Some drugs
Abnormal small intestine lining
Pathology

- **The inflammatory lesions** of the GIT are found in the small intestine, the area in great contact the ingested gliadin.
- **Increased No. of lamina propria mononuclear cells** underlying normal intestinal crypts & villi. This progress to further increased in cellular filtrate & development of **hypertrophic crypts** which elaborate crypt epithelial cells at a rate that compensates for the loss of epithelial villous cells. With further progression the inflammation reaches a **destructive stage** of Dz. characterized by **intense mononuclear infiltrate** associated with **crypt hyperplasia** that can no longer keep pace with the **loss of villous cells**; as a result, the villi become shortened or even flattened & the Pt. now develop the **characteristic mal absorption** of GSE.
- If the GSE inflammation prolonged, the mature lesion may progress to the **fibrotic or burned stage** in which destruction is permanent and the Pt no longer fully recovers when placed on a gluten-free diet.
1) Induction of T cells by APC which present gliadin peptides to T cells in the context of MHC Ags associated with GSE.

2) T cells [T\textsubscript{H1}] cells produce INF-\textgamma & TNF-\textalpha, which then act on intestinal macrophages to produce proinflammatory cytokines such as IL-1\beta & TNF-\alpha.

3) These cytokines induce fibroblast to produce metallo-proteinases that are the proximal cause of injury to the LP matrix supporting the villi.

The 2\textsuperscript{nd} mechanism:
1) T cells with TCR-bearing IEL recognize and lyses epithelial cells expressing gliadin peptides presented in the context of nonclassical MHC Ags.

2) B cells specific for gliadin also occur in lesions and give rise to characteristic s-IgA antigliadin Ab. Antibody for gliadin & an endogenous enzyme [transglutaminase] also occur. These entire Abs act to activate complement which subsequently amplifying the inflammatory process.

- These events seems to be genetically related to certain HLA molecules that enhance the Dz development and act as a risk factors for the Dz development such as HLA-B8, DR3 DQ2 particularly the latter which observed to participate in gliadin presentation to reactive T cells.
Epidemiology
Genetic factor enhances the chance for dz development (HLA-B8, DR3 DQ2). In addition, celiac disease is associated with other autoimmune syndromes. For example, as many as 7 percent of patients with type I diabetes also have gluten-sensitive enteropathy.

The clinical manifestations of CD vary markedly with the age of the patient, the duration and extent of disease, and the presence of extra intestinal pathology. Depending on the features at the time of presentation, together with the histologic and immunologic abnormalities at the time of diagnosis, CD can be subdivided into the following clinical forms.
Classical (typical) form
The so-called typical form of CD is present characteristically between
1) 6 and 24 months of age.
2) Symptoms begin at various times after the introduction of weaning foods containing gluten. Infants and young children typically present with chronic diarrhea, anorexia, abdominal distension, abdominal pain, poor weight gain or weight loss and vomiting.
3) Malnutrition can be severe if the diagnosis is delayed. Behavioral changes are common and include irritability.

Atypical forms
1) An increasing number of patients, especially at an older age, are being diagnosed with CD
2) without having typical gastrointestinal manifestations but there are various extra intestinal manifestations present such as dermatitis herpetic formis, anemia, osteoporosis, autoimmune hepatitis, dental enamel defects, recurrent aphthous stomatitis, epilepsy, and neuropathy.
3) Serology for CD is positive and biotic findings confirm the diagnosis.

Silent form
Silent celiac disease patients are those who are asymptomatic but small intestinal biopsy show villous atrophy. Silent cases are detected by population screening and screening of first degree relatives of celiac disease, 10% of whom are found to have CD. Serological tests are positive in them.
Latent form

Latent (or “potential”) form is asymptomatic patients, with a normal or minimally abnormal mucosa. These individuals have a genetic susceptibility to CD and may also have positive autoimmune serology.

Refractory celiac disease (RCD)

is defined by persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6–12 months in the absence of other causes of non-responsive treated celiac disease and overt malignancy

Celiac disease prevalence is increased in at-risk conditions such as family history of celiac disease, autoimmune diseases, especially type1diabetes (T1D) and thyroiditis, IgA deficiency, and some genetic syndromes.

The clinical course of GSE is dominated by gastrointestinal tract symptoms relating to malabsorption. The GIT manifestations are consist of weight loss, diarrhea, and symptoms due to nutritional deficiencies and in children growth failure.
Diagnosis

1. Small intestine biopsy

The most relevant feature of the disease was histological change, and histology became the gold standard for diagnosis. The diagnosis required three small bowel biopsies—the first during the gluten containing diet, which had to show “flat” mucosa; the second, during gluten free diet which showed improvement in villous structure, and the third, at gluten challenge 2 years later which had to show histological relapse.

The degree of the intestinal lesion is defined on the basis of the widely used Marsh-Oberhuber classification, it ranges from type 0 (Marsh 0) to Marsh type 4:
Type 0 concerns the normal stage of the small bowel mucosa.

Type 1 or infiltrative lesion is normal mucosal architecture in which the villous epithelium is infiltrated by small, non mitotic intraepithelial lymphocytes and it is characteristically present in first-degree relatives of children with celiac disease.

- **Type 2, or hyperplastic lesion**, consists of a type 1 lesion with enlarged crypts.
- **Type 3 or destructive lesion** is synonymous with the typical flat mucosa of CD and it is subclassified according to the different degrees of villous atrophy present:
  - Marsh type 3a, with partial villous atrophy;
  - Marsh type 3b, in the presence of subtotal villous atrophy; and
  - Marsh type 3c, when total villous atrophy is present.

- **Marsh type 4 or hypoplastic lesion** (total villous atrophy with crypt hypoplasia) represents the extreme end of the gluten-sensitivity spectrum and an irreversible lesion is present in some adult CD patients whose small bowel mucosa is unresponsive to gluten withdrawal: the so-called refractory CD.
Anti-gliadin antibodies (AGA) are not specific for CD as they are also found in healthy individuals and patients with other gastrointestinal diseases such as gastritis, gastroenteritis and irritable bowel syndrome, except in children younger than 2 years of age, in whom anti-gliadin antibodies measure is more sensitive test.

IgG-AGA is very sensitive but less specific;
IgA-AGA is less sensitive but more specific.

Their use in combination can give results of a high detection rate. Several methods have been used to analyze AGA, but currently ELISA is the most used method.

- Anti-endomysial antibodies (EMAs) are used as the “gold standard” for CD screening because of their high sensitivity and specificity. The test was developed in the early 1980s and rapidly gained use as part of “a celiac panel” by commercial labs in combination with AGA IgG and IgA. IgA-EMA and IgG-EMA are measured by indirect immunofluorescence, using tissue sections from either monkey esophagus or human umbilical cord. Its major drawbacks are false negatives in young children, and in the hands of an inexperienced laboratory because of the subjective nature of the test. Also IgA-EMA give false negative in patients with IgA deficiency.
Anti-tissue transglutaminase (tTG) antibodies are more specific have shown to be correlated with mucosal damage and are used widely in CD screening. IgG-tTG and IgA-tTG were used in combination as a screening test for celiac disease to assess IgA deficiency.

ELISA is the most used method to analyze tTG. However, it represents an improvement over the anti endomysial antibody assay because it is inexpensive, rapid and easy to perform.

- Anti-reticuline antibody is best detected by an indirect immunofluorescent method using unfixed cryostat sections of rat liver and kidney as antigens. IgA class reticulin antibodies react with connective tissue fibers and are found in 60% of celiac disease patients. IgG class reticulin antibodies are occasionally found in other disease states, especially bullous dermatoses and in some normal subjects.
Genetic testing

Up to 95% of patients with celiac disease are positive for HLA-DQ2, and most of the remaining patients are positive for HLA-DQ8. However, these alleles are also found in 40% of the general population. Although HLA-DQ2 and HLA-DQ8 are necessary in the disease process, they alone are not sufficient for celiac disease to develop. HLA testing has a high negative predictive value and can be useful in certain situations, such as when a diagnosis is unclear, when serologic testing or biopsy is performed in patients on a glutenfree diet, or in determining which family members to screen for celiac disease.
Serological Tests:

- Anti-tissue transglutaminase Antibody (TTG)
- IgA anti-endomysial Antibody (EMA) if TTG is positive
- Gliadin antibodies (not recommended, low sensitivity)
- Endoscopy with small bowel biopsy
- Imaging (at time of diagnosis and as warranted)
- Hematological & Biochemical Tests
  - Complete Blood Count with platelets
  - Iron studies (Serum Iron, TIBC, Ferritin)
  - Serum Vitamin B12
  - Serum Folate
  - Calcium
  - Phosphate
  - Renal Function tests (Blood Urea Nitrogen, Creatinine)
  - Liver Function Tests (AST, ALT, Albumin, Alk Phos).
Treatment

The only proven treatment for celiac disease is strict and life-long adherence to a gluten-free diet. All food and drugs that contain gluten from wheat, rye, barley, and their derivatives must be eliminated because even small amounts can be harmful.
Clinical Immunology 4ed stage
Dr. Thabit moath Le No 8
**Inflammatory bowel disease**

It is a chronic inflammatory disease of gastrointestinal tract due to immune response to the commensal microflora in the lumen of basal consistent and may be divided into two major groups:

- Crohn's disease
- Ulcerative colitis

**Crohn's disease** also known as granulomatous colitis and regional enteritis, it is classified as a type of inflammatory bowel disease, in which the body immune system attacks the gastrointestinal tract, causing a transmural inflammation, that may affect any part of the gastrointestinal tract from mouth to anus. It is onset patient between 15-30 year, males and females are equally affected.

Most gastroenterologists categorize the presenting disease by the affected areas:

- **Ileocolic Crohn's diseases**, which affect both the ileum (the last part of the small intestine that connect to the large intestine) and the large intestine, accounts for 50% of cases.
- **Crohn's ileitis**, affecting the ileum only, accounts for 30% of cases.
- **Crohn's colitis**, affecting the large intestine, accounts for the remaining 20% of cases and may be difficult to distinguish from ulcerative colitis.
However, individual affected by the disease rarely fall outside these three classification, being affected in other parts of the gastrointestinal tract such as the stomach and esophagus. Crohns disease may also be categorized by the behavior of disease as it progresses. There are three categories of disease presentation in Crohns disease:

- **Stricturing disease**: narrowing of the bowel which may lead to bowel obstruction or changes in the caliber of the feces.
- **Penetrating disease**: creates abnormal passageways (fistulae) between the bowel and other structures such as the skin.
- **Inflammatory disease**: cause inflammation without causing stricture or fistulae.

**Causes**

- **Genetic factor**: many studies that is suggested relationship between genetic and Crohns disease such as mutation in gene nucleotide-binding oligomerisation domain 2 (NOD2 gene) on chromosome 16.
- **Environmental factor**: by diet, smoking, drugs, hormonal contraception.
• **Immune system:** abnormalities in immune system causes Crohns disease and the inflammation that is occur in this disease causes activation of TH1 by an overproduction of IL-12 by macrophages and of IFN-γ by T lymphocytes.

• **Microbes:** there are many bacteria causes of Crohns disease such as Mycobacterium ovum, Yersinia spp and Listeria spp.

**Clinical Features**

A. **Gastrointestinal Features**

• Abdominal pain.
• Diarrhea may be bloody or may not be bloody, is different according to the part of the small intestine or large intestine, in ileitis large-volume watery feces, while, in colitis small volume semisolid or watery feces.
• Vomiting & nausea.
• Perianal discomfort (itching around the anus).
• Aphthous of mouth (ulceration of mouth).
B. Systemic Features
• In children causes growth failure, acute myelogenous leukemia in blood (myeloid) and lymphoma (cancer of lymph).
• In adult causes weight loss.

C. Extraintestinal Features
• In the eye, the inflammation of the interior portion of the eye is called uveitis or white part of the eye called episcleritis, both can lead to loss of vision if untreated.
• In the skin cause erythema nodosum (red nodules or subcutaneous tissue) or pyodermagangrenosum (ulcerating nodules).
• In the blood causes blood clotting especially painful of the lower legs can be a sign of deep venous thrombosis.
• Difficult breathing may be a result of pulmonary embolism.
• Autoimmune hemolytic anemia.
• Some neurological disease such as neuropathy & depression.
• Inflammation of one or more joints (arthritis).
• Osteoporosis increased risk of bone fracture.

**Ulcerative colitis**

*Ulcerative colitis* is confined to the colon and affects the mucosal layer only and causing a continuous inflammation. It is result of immune response to commensal microflora with $T_h2$ profile, through there is an increase of the $T_h2$ cytokine IL-5. Favouring a $T_h2$ pattern is the fact that ulcerative colitis is associated with the production of various autoantibodies, such as perinuclear anti-neutrophil cytoplasmic antibody (PANCA) and anti-tropomyosin.
Clinical Features

A. Gastrointestinal Features

- The clinical presentation of ulcerative colitis depends on the extent of the disease process. Patients usually present with diarrhea mixed with blood [Relapsing rectal bleeding] and mucus, of gradual onset.
- They also may have signs of weight loss, and blood on rectal examination.
- The disease is usually accompanied with different degrees of abdominal pain, from mild discomfort to severely painful cramp [Tenesmus].
B. Extraintestinal Features

- Aphthous ulcers of the mouth
- Ophthalmic (involving the eyes): Iritis or uveitis
- Musculoskeletal: Seronegative arthritis, Ankylosing Spondylitis, Sacroiliitis
- Cutaneous (related to the skin): Erythema nodosum, Pyoderma gangrenosum
- Deep venous thrombosis and pulmonary embolism
- Autoimmune hemolytic anemia
- Clubbing, a deformity of the ends of the fingers
- Primary Sclerosing Cholangitis, a distinct disease that causes inflammation of the bile ducts
1. In both inflammatory bowel diseases, the key diagnostic procedures are radiologic, endoscopic and histologic.

2. In Crohn's disease, typical laboratory findings include anemia (chronic disease, iron deficiency, vitamin B12 deficiency, folate deficiency), leukocytosis, thrombocytosis, elevation of the sedimentation rate, hypoaalbuminaemia and electrolyte imbalance in the presence of severe diarrhea. The measurement of C-reactive protein appears to be of use in monitoring the progress of the disease.

3. While, in ulcerative colitis, the laboratory findings are mostly non-specific, reflecting blood loss and inflammation, and include anemia, leukocytosis, elevated sedimentation rate and C-reactive protein levels. Seventy percent of patients with ulcerative colitis, but not with Crohn's disease, have been reported to have in their sera an anti-neutrophil cytoplasmic antibody (ANCA) that give a characteristic perinuclear staining (PANCA) that can also be seen in primary sclerosing cholangitis.

4. General stool examination for occult blood.
<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease site</td>
<td>Colon</td>
<td>Any part of gastrointestinal tract</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Mucosal</td>
<td>Transmural, granulomatous</td>
</tr>
<tr>
<td>Cytokine profile</td>
<td>$T_{H2}$</td>
<td>$T_{H1}$</td>
</tr>
<tr>
<td>ANCA positivity</td>
<td>50–80%</td>
<td>5–20%</td>
</tr>
</tbody>
</table>
Clinical Immunology
4ed stage
Dr. Thabit moath
Le No 9
Helicobacter pylori associated Chronic Gastritis & Mucosa-Associated Lymphoid Tissue Lymphoma (MALT)

Gastritis is a histological term that describes stomach inflammation resulting from toxic exposures, infection, idiopathic inflammation, and autoimmunity. The most common cause of gastritis is *H pylori* infection. Other causes include acid reflux, prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDS), alcohol use, and tobacco use, all of which can irritate the lining of the stomach. Severe illness and radiation therapy can also cause gastritis.
**Erosive gastritis** is most commonly caused by alcohol use, tobacco use, and prolonged use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDS). Severe illness and consumption of caustic substances have also been associated with the development of erosive gastritis. The most common cause of chronic, **nonerosive gastritis** is a stomach infection caused by Helicobacter pylori (H pylori), a type of bacteria found in up to half of all people in industrialized nations.
Symptoms

The signs and symptoms of gastritis vary among individuals. If infection with H. pylori bacteria is the cause, symptoms will remain as long as the infection is untreated. H. pylori is uniquely adapted to the acidic environment of the stomach through its ability to metabolize urea to ammonia, which provides a buffered microenvironment that allows prolonged asymptomatic colonization.

Some people with gastritis have no symptoms at all, while others may have burning abdominal pain, Loss of appetite, nausea with or without vomiting.

In some cases, gastritis can be life threatening, with symptoms including:

- Bloody stool (blood may be red, black, or tarry in texture)
- Severe abdominal pain
- Vomiting blood or black material (resembling coffee grounds)
Although acute infection can cause abdominal pain and dyspepsia, there is typically no clinical recognition of acute infection. Rather, the burden of H. pylori results from chronic infection of the stomach. The development of peptic ulcer disease and adenocarcinoma caused by chronic H. pylori infection correlates with the anatomical distribution of inflammation. When H. pylori chronic gastritis affects the antrum predominantly, there is an association with duodenal ulcers, increased serum gastrin levels and excess acid production, and no gastric mucosal atrophy. However, when H. pylori affects the body and the antrum in a confluent or patchy manner, intestinal metaplasia develops, oxyntic mucosa atrophies, and acid production decreases. This latter type of H. pylori chronic gastritis is associated with gastric ulcerations and increased risk for adenocarcinoma and mucosa-associated lymphoreticular tissue (MALT) B-cell lymphoma. Although eradication of H. pylori can reverse the mucosal atrophy and restore acid production in this setting, mucosal restoration occurs only in a minority of patients and does not necessarily reverse the intestinal metaplasia.
Immune pathophysiology

Although there are many pieces of evidence to support immune mechanisms for the persistence of HP infection in the stomach, data suggest that pro-regulatory effects of H. pylori infection, including local IL-10 production, increases in regulatory T cells (Tregs) in the gastric mucosa and increased antigen-presenting cell (APC) phagocytosis of apoptotic cells all contribute to persistence of chronic H. pylori gastritis.
Diagnosis

Active disease can be diagnosed with endoscopic biopsy, which has high sensitivity and specificity, while simultaneously assessing peptic and malignant complications. Noninvasive testing for *H. pylori* infection includes serum antibody detection (best used in highly endemic areas to predict active infection), urea breath testing (limited by expense and possible false-positive results), and fecal antigen testing (which has potential advantages in the setting of intestinal metaplasia and after antibiotic treatment).
Treatment

Once H. pylori infection is diagnosed, there are many effective eradication therapies that need to be tailored to patients’ drug tolerance and allergy history as well as local antibiotic resistance patterns. In general, a 14-day course with a proton pump inhibitor (histamine 2 [H2] blockers may be substituted) and two antibiotics (clarithromycin with amoxicillin or metronidazole) is recommended as first-line treatment. Alternative regimens, including bismuth or sequential therapy, may be needed in cases of antibiotic resistance. Eradication of infection can be confirmed by either invasive or noninvasive (but not serum antibody) methods.
Clinical Immunology
4ed stage
Dr. Thabit moath
Le No 10
Clinical Immunology
4ed stage
Dr. Thabit moath
Le No 10
Pernicious Anemia

Pernicious anemia (PA) is a megaloblastic anemia caused by a deficiency of vitamin B12 resulting from malabsorption. Impaired(week) absorption is the result of defective intrinsic factor (IF) secretion. This is due to atrophy of the gastric mucosa caused by autoimmune reactions to gastric parietal cells and their products. Pernicious anemia occurs in equal numbers in both men and women. Most patients with pernicious anemia are older, usually over 60 years. Occasionally, a child will have an inherited condition that results in defective intrinsic factor. Virtually all patients will have gastric parietal cells antibody targeting antigens in these canaliculi, which are the intracellular channels carrying hydrochloric acid into the gastric lumen and its major target is the α subunit of the proton pump (H+, K+, ATPase), an enzyme composed of two transmembrane components, the α and β subunits. In addition, there are at least two types of antibody against intrinsic factor: blocking and binding antibodies; the blocking type reacts with the combining site for vitamin B12 on IF and is found in most patients (over 70%), while the binding antibody reacts with other epitopes on IF (whether this is free or complexed to vitamin B12) and is present in some 60% of patients.
During the course of the digestion of foods containing B12, the B12 becomes attached to a substance called intrinsic factor. Intrinsic factor is produced by parietal cells that line the stomach. The B12-intrinsic factor complex then enters the intestine, where the vitamin is absorbed into the bloodstream. In fact, B12 can only be absorbed when it is attached to intrinsic factor.

In pernicious anemia, this process is impaired because of loss of parietal cells, resulting in insufficient absorption of the vitamin. So, the vitamin passes out of the body as waste. Although the body has significant amounts of stored B12, this will eventually be used up. At this point, the symptoms of pernicious anemia will develop.
Causes
Intrinsic factor is produced by specialized cells within the stomach called parietal cells. When these parietal cells shrink in size (atrophy), they produce less intrinsic factor. Eventually, the parietal cells stop functioning altogether. Other important products of parietal cells are also lessened, including stomach acid, and an enzyme involved in the digestion of proteins. Other conditions that interfere with either the production of intrinsic factor, or the body's use of B12, include conditions that require surgical removal of the stomach, or poisonings with corrosive substances which destroy the lining of the stomach. Certain structural defects of the intestinal system can result in an overgrowth of normal bacteria. These bacteria then absorb B12 themselves, for use in their own growth. A B-12 deficient state, may be caused by infection with the tapeworm Diphyllobothrium latum, possibly due to the parasite's competition for vitamin B-12. Various conditions that affect the part of the intestine (the ileum), from which B12 is absorbed, can also cause anemia due to B12 deficiency. These ileum-related disorders include tropical sprue, Crohn's disease, tuberculosis.
Symptoms

B12 is required for the proper formation of red blood cells. **Without B12, red blood cell production is greatly reduced.** Those red blood cells that are produced are **abnormally large and abnormal in shape.** Because **red blood cells** are responsible for **carrying oxygen** around the body, decreased numbers (termed anemia) result in a number of symptoms see figure
Symptoms of Anemia

Central
- Fatigue
- Dizziness
- Fainting

Blood vessels
- Low blood pressure

Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack

Spleen
- Enlargement

Respiratory
- Shortness of breath

Muscular
- Weakness

Intestinal
- Changed stool color

Skin
- Paleness
- Coldness
- Yellowing

Eyes
- Yellowing

Red = in severe anemia
Diagnosis
Tests that may be used to diagnosis pernicious anemia include
- Blood smear reveals abnormally large red blood cells.
- White blood cells and platelet counts may also be decreased in number.
- Reticulocyte count will be low in number.
- Serum vitamin B12 level will be low.
- Schilling test, in this test, a patient is given radioactive B12 under two different sets of conditions: once alone, and once attached to intrinsic factor. Normally, large amounts of B12 are absorbed through the intestine, then circulate through the blood, and enter the kidneys, where a certain amount of B12 is then passed out in the urine. When a patient has pernicious anemia, the dose of B12 given by itself will not be absorbed by the intestine, so it will not pass into the urine. Therefore, levels of B12 in the urine will be low. When the B12 is given along with intrinsic factor, the intestine is able to absorb the vitamin. Urine levels of B12 will therefore be higher.
Immunology, specifically anti-parietal cell antibody (APCA) and intrinsic factor antibody (IFA). APCAs bind to the alpha- and beta-subunits of the membrane-bound H(+)K(+)-ATPase. In contrast, IFAs bind directly to intrinsic factor, blocking its ability to bind vitamin B12 and can be detected by means of immunofluorescence, enzyme-linked immunosorbent assay - currently the most commonly used method, and radioimmunoprecipitation assay (RIA). APCA can be found in 85-90% of patients with PA. Their presence is not sufficient for diagnosis, because they are not specific for PA as diseases. APCA are more prevalent in the serum of patients with T1D, autoimmune thyroid diseases, vitiligo, celiac disease. So that a combination of PCA and IFA testing was the optimal strategy for the evaluation of patients with suspected PA
Diabetes mellitus
Diabetes is a state of high blood sugar (hyperglycemia) that can have many underlying causes and is classified into:

1. **Insulin-dependent diabetes mellitus** (IDDM) or type 1.
2. **Non-insulin-dependent diabetes mellitus** (NIDDM) or type 2.
3. **Gestational diabetes mellitus**.

**Type 1 diabetes mellitus**
Type 1 diabetes mellitus (type 1 DM) is a major clinical problem in both children and adults. It is an organ-specific autoimmune disease represents 10-15% of all diabetes. Healthy human islets of Langerhans are composed of a core of some 80% β cells (making the glucose-regulating hormone insulin), with a mantle of other endocrine cells types, producing glucagon (α cells), somatostatin (δ cells) and pancreatic polypeptide (PP cells) making up the remainder.

In type 1 DM, the hyperglycemia results from insufficient insulin secretion by β cells in the islets of Langerhans of the pancreas.
Causes

1. **Genetic**: DR3/DQ2 or DR4/DQ8 haplotypes have strong link for the incidence of the disease, but other genetic associations (non HLA) are CTLA-4 (cytotoxic lymphocyte associated protein 4) also found in many family that play a role in the onset of type 1DM.

2. **Environmental factors**: Seasonal variation in the incidence rate (peaks in autumn and winter).

3. **Infection with pathogens** that have specific tropism toward the pancreatic tissue, mumps and coxsakie viruses. Similarities in the protein sequence of these viruses and certain islet cell cytoplasmic (ICA), glutamic acid decarboxylase (GAD) would initiate molecular mimicry mechanism in tolerance breakdown.
Immunopathogenesis
A virus infection in the pancreatic β islets cells leads to inflammation, damaged and releasing β cells antigens, their recruit antigen presenting cells (dendritic cells) which capture the virus protein and auto antigens released from the damaged β islets cells to local lymph node and present them to T cells. T cells are activated to eradicate the virus. Inadvertently, T cells are activated against β cells and the slow process of β cells damage starts. In type 1 DM insulin production is failed due to destruction of β cells in the islets of Langerhans in pancreatic tissue without any destruction in the other cells as (α or δ cells) which is mediated by specific immune response).
<table>
<thead>
<tr>
<th>Autoantigens</th>
<th>Islet specific</th>
<th>Function</th>
<th>Autoantibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Yes, and β cells specific</td>
<td>Regulates glucose</td>
<td>Insulin autoantibody (IAA)</td>
</tr>
<tr>
<td>Glutamic acid decarboxylase</td>
<td>No, present in other islet cells and CNS</td>
<td>Catalyses synthesis of γ-aminobutyric acid (GABA), a negative neurotransmitter probably regulates insulin release.</td>
<td>Glutamic acid decarboxylase autoantibody (GADA)</td>
</tr>
<tr>
<td>Islet tyrosine phosphatase</td>
<td>No, present in other islet cells and CNS</td>
<td>Unknown</td>
<td>Insulinoma-2 associated autoantibody (IA-2A)</td>
</tr>
<tr>
<td>Zinc transport 8</td>
<td>Yes, and β cells specific</td>
<td>Zinc transport</td>
<td>Zinc transport 8 autoantibody (ZnT8A)</td>
</tr>
</tbody>
</table>
**Symptoms**

Many pre- or subclinical stages occur in the DM patient before clinical diagnosis can be done:

1. **Stage 1**: the cell mass and function of β cells is normal but individuals who carry genetic susceptibility alleles to type 1 suffer exposure to an environmental stimulus triggering islets inflammation (insulitis). The release of sequestered or altered self antigens explains in part the later development of islet Autoantibodies that mark the recognition of stage 2.

2. **Stage 2**: serological evidence of humoral and cell-mediated autoimmunity indicated by the appearance of different types of autoantibody as islet cell cytoplasmic autoantibody (ICA), glutamic acid decarboxylase autoantibody (GADA), insulinoma-2 associated autoantibody (IA-2A) or insulin autoantibody (IAA). This occurs without any clinical metabolic signs. However, during this stage, there can be a 50% decline in β cells mass without detectable abnormalities by any form of glucose tolerance testing.
3. Stage 3: The earliest functional β cells abnormalities which manifestation by the intravenous glucose tolerance test (IVGTT) which decrease.
4. Stage 4: intolerance to oral glucose challenges appears as indicated by oral glucose tolerance test (OGTT).
5. Stage 5: after 1-2 years of glucose intolerance upon oral testing, atypical history of polyuria, polydipsia, polyphagia with weight lose are identified. Finally by a true hyperglycemia a full diagnosis can be done.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 11
Renal disease

Introduction

The glomerulus is the communication point between the bloodstream and nephron, the functional unit of the kidney. It is composed of the glomerular capillaries and Bowman’s capsule of the nephron. Fluid from the blood in the glomerular capillaries passes into the Bowman’s capsule and then enters the tubules where it is processed to form urine. Each kidney has about 1 million nephrons that act together to complete the various functions including removing waste substances from the blood, regulating blood volume and blood pressure. If a significant number of nephrons are damaged, these functions will be significantly hampered. Mesangial cells among the glomerular capillaries regulate the blood flow in the capillaries. If these cells and layers of the glomerulus are damaged, glomerular filtration and therefore normal kidney functioning is impaired.
Renal diseases

Many renal diseases have underlying immunological mechanisms. Antibody-mediated effects are primarily involved. Other mechanisms may involve cell-mediated injury or cytotoxic antibodies. Immunological diseases of the kidney mainly affect the glomerulus, which is most likely due to its filter function. Circulating antibody-mediated renal diseases are induced in three mechanisms:-
1. Circulating performed immune complexes accumulate sub-endothelial on the capillary aspect of the basement membrane.

2. Antibodies may react in situ with the glomerular basement membrane.

3. Antigens of the visceral epithelial cells.

Antibody deposits can cause direct damage to epithelial or endothelial cells of glomerulus due to complement activation and pore formation. On the other hand, the antibodies can also bind to the FC receptors of monocytes, macrophages, granulocytes and platelets. This leads to the activation, or in the case of platelets aggregation of the cells. The glomerular damage can cause two distinct symptom complexes:
The nephrotic syndrome:

The nephritic syndrome:

<table>
<thead>
<tr>
<th>Typical Features</th>
<th>Nephrotic</th>
<th>Nephritic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Insidious</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Edema</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Raised</td>
</tr>
<tr>
<td>Jugular venous pressure</td>
<td>Normal/low</td>
<td>Raised</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>May/may not occur</td>
<td>+++</td>
</tr>
<tr>
<td>Red blood cell casts</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Low</td>
<td>Normal/slightly reduced</td>
</tr>
</tbody>
</table>
Glomerulonephritis (GN)

Means inflammation in the kidneys either of the small blood vessels or of the glomeruli but includes a number of disorders that affect the structure and function of the glomerulus without any prominent inflammation. It is therefore also referred to as glomerular disease or glomerulopathy. In glomerulonephritis, various known and unknown causes trigger immune activity against the glomeruli which damages it. Diagnosing the pattern of GN is important because the outcome and treatment differs in different types.
Pathophysiology of Glomerulonephritis

Glomerulonephritis is known to be an immune reaction mediated by antigen-antibody complexes. An antigen is the trigger substance against which antibodies are formed by the immune system. The antibodies then bind with the antigen and this antigen-antibody complex can instigate a number of immune activities designed to protect the body. In the process, inflammation arises in whichever tissue that the targeted immune response is occurring. Although the exact cause of glomerulonephritis is not always understood, the mechanism by which it occurs is proposed in two different models –
1. Immune complex deposition
2. Circulating immune complexes.
   Other mechanisms may involve
3. cell-mediated injury or
4. cytotoxic antibodies.

In **immune complex deposition**, it is believed that antibodies are directed against antigens that are “planted” in the glomerulus or against antigens that are normal components of the glomerulus, specifically the glomerular basement membrane (GBM). The immune activity is therefore specifically targeted at the glomerulus.
With circulating immune complexes, the antigen-antibody complexes are circulating in the bloodstream and eventually reach the glomerulus during glomerular filtration. These complexes form in the backdrop of several autoimmune or infectious diseases and the antigen may be endogenous (created within the body) or exogenous (from foreign matter or microorganisms) in nature. In these cases, immune activity is targeted at the circulating immune complex and can lead to inflammation at other sites in the body as well as the glomerulus.

In response to the inflammation, different histologic alterations may be seen in the glomerulus. This includes:

- Increase in the number of cells (capillary endothelium or mesangial cells)
- Thickening of the basement membrane
- Tissue degeneration – hyalinosis and sclerosis.

Types of Glomerulonephritis

1- Glomerulonephritis may be primary or secondary.

**Primary glomerulonephritis** arises on its own without any other underlying disease. **Secondary glomerulonephritis** occurs as a consequence of some other disease, which may not even involve the kidney.

2- Acute and Chronic Glomerulonephritis

In acute glomerulonephritis, the condition starts suddenly and the tissue damage progresses rapidly. With chronic glomerulonephritis, the condition develops gradually and damage becomes extensive after months or years.
Signs and Symptoms of Glomerulonephritis

• Hematuria (blood in the urine) which may appear as pink-colored or brownish urine.
• Proteinuria (protein in the urine) which may present as foamy urine (frothy).

• Edema (swelling) most prominent in the face, hands, abdomen and feet.

• Hypertension (high blood pressure)

• Azotemia (high urea levels in the blood) which leads to various additional signs and symptoms (uremia).
Glomerulonephritis may lead to a collection of clinical features grouped together as glomerular syndromes and includes:

- **Nephrotic syndrome** – proteinuria (protein in urine), hypoalbuminemia (low blood proteins), edema (swelling due to fluid retention), hyperlipidemia (high blood lipids), lipiduria (lipids in the urine).

- **Nephritic syndrome** – hematuria (blood in urine), azotemia (high urea levels in blood), proteinuria, oliguria (large volume of urine), edema, and hypertension (high blood pressure).

- **Rapidly progressing glomerulonephritis** – nephritis (kidney inflammation), proteinuria, and acute renal failure.

Additional signs and symptoms of glomerulonephritis may include:

- Anemia
- Fatigue
- Nausea and vomiting
- Paleness and/or yellowing of the skin
- Itching of the skin
- Dehydration
Clinical immunology

4\textsuperscript{th} stage

Dr. Thabit Moath

Le No 12
Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) describes a group of diseases with aggressive glomerular injury which may be irreversible if not treated early (e.g. antiglomerular basement membrane disease, anti-neutrophil cytoplasmic antibody associated glomerulonephritis).
Anti-gglomerular basement membrane disease

Anti–glomerular basement membrane (anti-GBM) disease is an autoimmune disorder characterized by the presence of circulating pathogenic autoantibodies directed against proteins in the glomerular and alveolar basement membranes. In the kidneys, binding of these autoantibodies with the GBM results in activation of the complement cascade and can lead to rapidly progressive glomerulonephritis. In Goodpasture syndrome, (or anti-GBM disease) is a rare, life-threatening autoimmune disease that affects the lungs and the kidneys. It happens when the immune system mistakenly attacks a protein called collagen because it recognizes it as a foreign substance. In Goodpasture syndrome, the body produces proteins (antibodies) that attach to the collagen in certain parts of the lungs and the kidneys. When they attach to the collagen, these antibodies cause severe inflammation and destruction of those tissues. An early and precise diagnosis of anti-GBM disease is extremely important for preventing death and preserving renal function. If not treated promptly, anti-GBM disease can cause serious complications, such as
1. Severe kidney inflammation, which can quickly lead to kidney failure.
2. Severe bleeding in the lungs, which can cause respiratory failure.

Acute glomerulonephritis mediated by anti-glomerular basement membrane (anti-GBM) antibody account for about 1-2% of all cases of glomerulonephritis. Anti-CBM nephritis is more common in men and in those who possess HLA-DR2.

The target Ag is the \( \alpha_3 \) chain of type IV collagen, a major constituent of the GBM.

Lung damage results from antibodies to antigens common to both alveolar and glomerular basement membranes. In Goodpasture’s syndrome, respiratory symptoms often precede renal disease by 1 year or longer. Haemoptysis, usually leading to anemia, is a prominent feature and the sputum typically contains haemosiderin-laden macrophages. Biopsies show intra-alveolar haemorrhage and necrotizing alveolitis.

Although the cause is unknown, anti-GBM disease follows upper respiratory tract infections in 20-60% of patients, or exposure to certain hydrocarbons. These agents may damage alveolar basement membrane, generating new and potent antigens able to stimulate autoantibody production. Alternatively, the agent responsible (e.g. a virus may cross-react with basement membrane antigens.)
ANCA vasculitis is an autoimmune disease affecting **small blood vessels in the body**. It is caused by autoantibodies called ANCAs, or **Anti-Neutrophilic Cytoplasmic Autoantibodies**. ANCAs target and attack a certain kind of **white blood cells** called **neutrophils**. They target a part of neutrophils called the cytoplasm (the inside of the cell.)

When ANCAs (the autoantibodies) attach to neutrophils, it makes the neutrophils attack small blood vessels in the body, and the blood vessels become swollen and inflamed.

When blood vessels in the kidney are affected, it can cause blood and protein to leak into the urine, as well as kidney damage (kidney function gets worse).

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis is the most frequent cause of rapidly progressive glomerulonephritis and is usually classified as a **pauci-immune type characterized by glomerular necrosis and crescent formation**.
Autoantibodies in ANCA

There are 2 main kinds of autoantibodies that can be involved in ANCA vasculitis.

1. P-ANCA is called (perinuclear ANCA). This type of autoantibody usually targets and attaches to something called MPO (myeloperoxidase), which is inside of neutrophils.
2. C-ANCA is called (cytoplasmic ANCA). This type is usually targets and attaches to something called proteinase 3 (PR3), which is also inside of neutrophils.
Symptoms

There are many different symptoms that can occur in ANCA vasculitis. If the kidneys are affected:

- Blood in the urine (may appear red or more often tea-colored)
- Foamy urine (due to protein in the urine)
- New or worsened high blood pressure
- Decreased kidney function or kidney failure – this often does not cause a lot of symptoms until it is more advanced/severe, but symptoms can include fatigue, nausea/vomiting, poor appetite, metallic taste
Diagnosis of ANCA

1- Blood tests for kidney function (creatinine), urine tests for blood and protein, and looking at the urine under a microscope

2- Although a positive ANCA test (on bloodwork) can be very helpful in pointing to a diagnosis of ANCA vasculitis, it is not a perfect test and cannot determine the diagnosis alone.

3- A kidney biopsy can confirm the diagnosis.
Clinical immunology

Fourth stage

Lecture :-( 11 )

P-ANCA Pattern

C-ANCA Pattern
(A) Light microscopy showing thickened glomerular capillary walls and a fibrocellular crescent (PAM stain, ×400).

(B) Immunofluorescence staining revealing deposition of IgG along glomerular capillary walls (×200).

(C) Electron micrograph showing thickened glomerular basement membrane with diffuse subepithelial deposits and foot process effacement (×6500).
**Treatment**

In general, treatment for ANCA vasculitis involves 2 parts.

The first part is called induction therapy, which is aimed at trying to get the disease controlled and into remission.

The second part of treatment is called maintenance therapy. Maintenance therapy involves continuing immunosuppressive medications to keep the disease in remission and decrease the chance that it will come back (relapse).

These are some of the treatments/medicines that can be used:

1- **Corticosteroids**: Drug works by decreasing the movement of polymorphonuclear leukocytes (PMNs) to sites of cellular and tissue injury to decrease inflammation.

2- **Cyclophosphamide**: Drugs of this class suppress the natural immune system including B and T lymphocyte activity and function.

3- **Rituximab**: is a medicine that reduces the number of immune cells in the body.

4- **Azathioprine**: Drugs of this class alter RNA and DNA, building blocks of all cells, resulting in blunting of the immune system.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 13
Membranous Glomerulonephritis
MN is one of the most common causes of nephrotic syndrome. When your immune system attacks the glomeruli in membranous nephropathy, it causes changes to the filters that lead you to lose large amount of protein into the urine. is a specific type of glomerulonephritis also known as membranous glomerulopathy, Membranous nephropathy and extra membranous glomerulonephritis. is a slowly progressive disease of the kidney affecting mostly people between ages of 30 and 50 years, usually white people (i.e., those of European, Middle Eastern, or North African ancestry).
Symptoms

The symptoms of MGN are different for everyone, and you may not have symptoms at all. If symptoms do develop, they typically include:

- swelling of the hands, feet, or face
- fatigue
- foamy urine
- an excessive need to urinate at night
- weight gain
- poor appetite
- blood in the urine
Causes of membranous nephropathy (MN)
Most cases of MN are now known to be caused by an antibody to a protein on the podocyte called the phospholipase A2 receptor (PLA2R). In most people with MN, the body’s immune (defense) system makes an antibody (a protein that normally helps fight infections). Instead of targeting an infection, these antibodies attack the podocytes. The podocytes stop retaining the proteins in the blood stream and allow them to leak into the urine.
Pathophysiology of Membranous Glomerulonephritis

MGN is caused by immune complex formation in the glomerulus. The immune complexes are formed by binding of antibodies to antigens in the glomerular basement membrane. The antigens may be part of the basement membrane, or deposited from elsewhere by the systemic circulation.

The immune complex serves as an activator that triggers a response from the C5b - C9 complements, which form a membrane attack complex (MAC) on the glomerular epithelial cells. This, in turn, stimulates release of proteases and oxidants by the mesangial and epithelial cells, damaging the capillary walls and causing them to become "leaky". In addition, the epithelial cells also seem to secrete an unknown mediator that reduces nephrin synthesis and distribution.
Diagnosis of membranous nephropathy (MN)

- **Blood test:** Taking a sample of blood to measure levels of fat and protein.

- **Glomerular filtration rate (GFR):** Studying a blood sample to measure kidney function.

- **Kidney biopsy:** Taking a small sample of kidney tissue with a needle and having a lab examine it to see if it contains an antibody associated with MN.

- **Urine test:** Measuring levels of protein and blood in your urine.

- **Antibody levels:** blood sample to measure the levels of the antibody against the phospholipase A2 receptor.
Treatment

For treatment of idiopathic membranous nephropathy, the treatment options include **immunosuppressive drugs** and

- **non-specific anti-proteinuric** measures such as **ACE inhibitors** (Angiotensin-converting enzyme (ACE) inhibitors) *(Captopril, Enalapril (Vasotec), Fosinopril, Lisinopril)* or **angiotensin II receptor blockers**. Given spontaneous remission is common, international guidelines recommend a period of watchful waiting before considering **immunosuppressive treatment**. \[18\] Likelihood of achieving spontaneous remission is much higher if anti-proteinuric therapy with ACE inhibitors or angiotensin II receptor blockers is commenced.
Post infection
Glomerulonephritis
Poststreptococcal glomerulonephritis (GN) is a kidney disorder that occurs after infection with certain strains of streptococcus bacteria. It is mainly seen in countries in which antibiotics for streptococcal infections are not widely available and accounts for about a third of cases of acute GMN. It is a disease of children aged 2–10 years, but adolescents and adults may be affected. Over 90% of cases are preceded by streptococcal infection of the throat or skin. Patients typically present with acute nephritis 7–12 days after a throat infection or about 3 weeks after a skin infection.
Symptoms

Symptoms may include any of the following:

- **Decreased urine output**
- Rust-colored urine
- Swelling (edema), general swelling, swelling of the abdomen, swelling of the face or eyes, swelling of the feet, ankles, hands
- Visible blood in the urine
- **Joint pain**
- **Joint stiffness or swelling**
Causes

Poststreptococcal GN is a form of glomerulonephritis. It is caused by an infection with a type of streptococcus bacteria. The infection does not occur in the kidneys, but in a different part of the body, such as the skin or throat. The disorder may develop 1 to 2 weeks after an untreated throat infection, or 3 to 4 weeks after a skin infection.

The condition is not common today because infections that can lead to the disorder are treated with antibiotics.
Pathophysiology

APSGN is an immune complex-mediated disease. Several mechanisms may participate in the pathogenesis of renal damage. Nephritogenic immune complexes are formed in circulation and deposited in the glomeruli; alternately, the antigen and antibody arrive separately and meet in or outside the glomerular basement membrane, causing in situ immune complex disease. Immune cell recruitment, production of chemical mediators and cytokines, and local activation of the complement and coagulation cascades drive an inflammatory response that is localized in the glomeruli. Glomerular deposition of circulating immune complexes depends on the antigen load, the antigen:antibody ratio, and the size of the immune complexes. In situ formation of immune complexes is favored by cationic antigens that have a charge-dependent facilitated penetration into the polyanionic glomerular basement membrane, and tend to occur in conditions of antigen excess.
Diagnosis

Laboratory investigations are the most useful in PSGN assessment.

- Evidence of a preceding streptococcal infection is determined by measuring **anti-streptolysin titer (ASO)**, and **anti-nicotinamide-adenine dinucleotidase (anti-NAD)** which tend to rise following pharyngitis. Other antibodies such as **anti-DNAse** B and **anti-hyaluronidase (AHase)** are usually elevated after both pharyngitis and skin infections. **ASO titer is the most frequently used test, while the most sensitive is the streptozyme test**; which includes measuring the titers of all the antibodies mentioned above. ASO titers can be falsely low in patients treated with antibiotics for streptococcal infections.

- Serum complement level (C3) is usually low due to its consumption in the inflammatory reaction. Mostly, the **decrease in C3 concentration** occurs before serum ASO has risen. Complement levels usually return to normal levels in 6-8 weeks.

- Urine analysis: shows macroscopic or microscopic hematuria, RBC casts, mild proteinuria. Only 5% of patients with PSGN have massive proteinuria that indicates nephrotic syndrome. White blood cell casts, hyaline, and cellular casts are usually present in the urine analysis.

- Renal Function Tests: Blood urea nitrogen and serum creatinine typically elevate during the acute phase. These values usually return to normal later.

**Renal biopsy is not recommended** for diagnosing patients with PSGN and is performed only when other glomerular pathologies are suspected.
Treatment

There is no specific treatment for this disorder. Treatment is focused on relieving symptoms.

- **Antibiotics**, such as penicillin, will likely be used to destroy any streptococcal bacteria that remain in the body.

- **Blood pressure medicines and diuretic drugs** may be needed to control swelling and high blood pressure.

- **Corticosteroids and other anti-inflammatory medicines** are generally not effective. You may need to limit salt in your diet to control swelling and high blood pressure.
IgA Nephropathy
IgA nephropathy is a chronic kidney disease. It progresses over 10 to 20 years, and can lead to end-stage renal disease. It is caused by deposits of the protein immunoglobulin A (IgA) inside the filters (glomeruli) in the kidney. It is one of the most common causes of primary glomerulonephritis in the world.

IgA nephropathy was first described by Berger and Hinglais in 1968, and is also known as Berger disease.

It accounts for about 10% of all cases of primary glomerular disease in the USA, 20% of cases in Europe and 30–40% in Asia.
Symptoms

IgA nephropathy usually **asymptomatic** in the early stages, so the disease can go unnoticed for years or decades. It's sometimes suspected when routine tests reveal protein and red blood cells in your urine that can't be seen without a microscope (microscopic hematuria).

Signs and symptoms of IgA nephropathy include:

- **Cola- or tea-colored urine (caused by red blood cells in the urine)**
- **Repeated episodes of cola- or tea-colored urine, and sometimes visible blood in your urine, usually during or after an upper respiratory or other infection and sometimes after strenuous exercise**
- **Foamy urine from protein leaking into your urine (proteinuria)**
- **Flank pain :- Pain in the one or both sides of your back below your ribs**
- **Swelling (edema) in your hands and feet**
- **High blood pressure (Hypertension)**
Pathophysiology

The disease derives its name from deposits of Immunoglobulin A (IgA) in a granular pattern in the mesangium (by immunofluorescence), a region of the renal glomerulus. The mesangium by light microscopy may be hypercellular and show increased deposition of extracellular matrix proteins.

There is no clear known explanation for the accumulation of the IgA. Exogenous antigens for IgA have not been identified in the kidney, but it is possible that this antigen has been cleared before the disease manifests itself. It has also been proposed that IgA itself may be the antigen.

The exact pathogenesis of IgA nephropathy is still not well defined. Current data implicate an important genetic factor, especially in promoting the overproduction of an aberrant form of IgA. The immunochemical aberrancy of IgA nephropathy is characterized by the undergalactosylation of O-glycans in the hinge region of IgA. However, such aberrant glycosylation alone does not cause renal injury.
The next stage of disease development requires the formation of **glycan-specific IgG and IgA antibodies** that recognize the under galactosylated IgA1 molecule. These antibodies often have reactivity against antigens from extrinsic microorganisms and might arise from recurrent mucosal infection. B cells that respond to mucosal infections, particularly tonsillitis, might produce the nephritogenic IgA1 molecule. With increased immune-complex formation and decreased clearance owing to reduced uptake by the liver, IgA1 binds to the glomerular mesangium via an as yet unidentified receptor. Glomerular IgA1 deposits trigger the local production of **cytokines** and **growth factors**, leading to the activation of mesangial cells and the **complement system**. Emerging data suggest that mesangial-derived mediators following glomerular deposition of IgA1 lead to **podocyte and tubulointerstitial injury via mesangio–podocytic–tubular crosstalk**. This Review summarizes the latest findings in the pathogenesis of IgA nephropathy.
Diagnosis

1- **ultrasound of the kidney** and **cystoscopy** are usually done first for an adult patient with isolated **hematuria**, to pinpoint the source of the **bleeding**. In children and younger adults, the **history and association with respiratory infection** can raise the suspicion of IgA nephropathy.

2- **A kidney biopsy is necessary to confirm the diagnosis.** The biopsy specimen shows **proliferation of the mesangium**, with **IgA deposits** on **immunofluorescence** and **electron microscopy**.

3- A **urinalysis** will show **red blood cells**, usually as red cell **urinary casts**. **Proteinuria**, usually less than 2 grams per day, also may be present.

4- Other **blood tests** done to aid in the diagnosis include **CRP (c reactive protein)** or **ESR**, **complement levels**, **ANA, and LDH** (**Lactate Dehydrogenase Test**).

  **Protein electrophoresis** and **immunoglobulin levels** can show increased IgA in 50% of all patients.
Treatment for IgA nephropathy

Treatment for IgA nephropathy includes medication to:

- **Control blood pressure** with angiotensin-converting enzyme (ACE) inhibitors, (Angiotensin-converting enzyme (ACE) inhibitors
- angiotensin receptor blockers (ARBs), or other medicines.
- **Remove extra fluid with a diuretic.**
- Control your immune system to lower kidney inflammation with prescribed steroids such as prednisone or cyclophosphamide.
- **Lower your cholesterol levels** with medications such as statins.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 15-14
Glomerulonephritis associated with systemic disease
A- Lupus Nephritis
B- Henoch-Schonlein Purpura
A- Lupus Nephritis :- Lupus is an autoimmune disease that triggers your immune system to attack your tissues. In addition to your kidneys, lupus can damage your brain, heart, joints, skin and other parts of your body.
Stages of Lupus Nephritis
Based on the kidney biopsy, will know the stages or classification of lupus nephritis. The six stages, or classes, are based on:

a- Cell changes in the glomeruli as seen under the microscope
b- Immune deposits seen on immunofluorescence
- Electronic microscopy
Stage 1: Minimal mesangial glomerulonephritis
- Minor kidney damage
- No obvious other signs or symptoms

Stage 2: Mesangial proliferative glomerulonephritis
- Some clear damage to the kidney
- Extra blood or protein in your urine that your health care team can detect with lab tests

Stage 3: Focal glomerulonephritis
- More damage that amounts to less than 50% of important blood vessels in your kidney
- Higher amounts of blood or protein in urine
- Possible high blood pressure

Stage 4: Diffuse proliferative nephritis
- Damage that amounts to more than 50% of important blood vessels in the kidney
- Blood or protein in urine
- Possible high blood pressure
- Possible need for dialysis as kidneys stop working properly
Stage 5: Membranous glomerulonephritis
  - Thickening of important parts of the kidney
  - Blood or protein in urine
  - Possible high blood pressure
  - Dialysis or possible kidney transplant

Stage 6: Advanced sclerotic
  - Damage to more than 90% of important kidney blood vessels
  - When treatment is possible, may need dialysis or kidney transplant
  - Plus other signs: Blood or protein in urine and high blood pressure
Symptoms of lupus nephritis

Symptoms of lupus nephritis tend to develop about five years after lupus symptoms first appear. But lupus nephritis can be the first — and sometimes the only — manifestation of systemic lupus erythematosus (SLE). Lupus nephritis can cause:

1. **Edema** (swelling due to fluid buildup) in your lower body or around your eyes.
2. **Fever** with no known cause.
3. **Hematuria** (blood in the urine).
4. **High blood pressure**.
5. Increased urination, especially at night.
6. **Joint pain** or swelling. **Muscle pain**.
7. **Proteinuria** (protein in the urine), which often causes your urine to look foamy.
8. Red skin rash on the face.
9. Weight gain due to excess fluid in your body.
Causes lupus nephritis

No one knows why some people with SLE develop lupus nephritis. Your family background and ancestry, medical conditions, and environmental factors such as exposure to chemicals or pollutants may all play a role in causing the disease.

Lupus nephritis usually gets worse over time, which can lead to kidney failure. The cause of lupus in most cases, however, is unknown.
Pathophysiology

Autoimmunity plays a major role in the pathogenesis of lupus nephritis. The immunologic mechanisms include production of autoantibodies directed against nuclear elements. The characteristics of the nephritogenic autoantibodies associated with lupus nephritis are as follows:

1. **Antigen specificity** directed against nucleosome or double-stranded DNA (dsDNA) - Some anti-dsDNA antibodies cross-react with the glomerular basement membrane

1. **Higher-affinity autoantibodies** may form intravascular immune complexes, which are deposited in glomeruli

1. **Cationic autoantibodies** have a higher affinity for the anionic glomerular basement membrane

1. **Autoantibodies of certain isotypes** (immunoglobulin [Ig] G1 and IgG3) readily Activate complement

These autoantibodies form pathogenic immune complexes intravascularly, which are deposited in glomeruli. Alternatively, autoantibodies may bind to antigens already located in the glomerular basement membrane, forming immune complexes in situ. Immune complexes promote an inflammatory response by activating complement and attracting inflammatory cells, including lymphocytes, macrophages, and neutrophils.
Diagnosis of lupus nephritis

The diagnosis of lupus nephritis depends on

1- blood tests.

2- urinalysis: a nephritic picture (i.e, symptoms of nephritic) is found and red blood cell casts, red blood cells and proteinuria is found.

3- X-rays.

4- ultrasound scans of the kidneys.

5- kidney biopsy.
Treatment of lupus nephritis

1. Corticosteroids: These strong anti-inflammatory drugs can decrease inflammation.

2. Immunosuppressive drugs: These drugs, which are related to the ones used to treat cancer or prevent the rejection of transplanted organs, work by suppressing immune system activity that damages the kidneys. They include azathioprine (Imuran), cyclophosphamide (Cytoxan), voclosporin (Lupkynis) and mycophenolate (Cellcept).

3. Medications to prevent blood clots or lower blood pressure if needed.

The goals of treatment for lupus nephritis are to:

1. Reduce inflammation in your kidneys.

2. Decrease immune system activity.

3. Block your body’s immune cells from attacking the kidneys directly or making antibodies that attack the kidneys.
Henoch-Schonlein Purpura
(HSP) is an acute immunoglobulin A (IgA)–mediated disorder characterized by a generalized vasculitis involving the small vessels of the skin, the gastrointestinal (GI) tract, the kidneys, the joints, and, rarely, the lungs and the central nervous system (CNS). It most commonly occurs in children.
Symptoms of Henoch-Schönlein Purpura

1- The main symptom is a spotty rash with numerous small bruises rash

2- Joint pain and swelling

3- Abdominal pain

4- Blood in urine.

Before these symptoms begin, patients may have two to three weeks of fever, headache, and muscular aches and pains. Rarely, other organs, such as the brain, lungs, or spinal cord may be affected.
Causes and Risk Factors for Henoch-Schonlein Purpura

The exact cause of HSP is not known. The body's immune system is believed to play a role in targeting the blood vessels involved. An abnormal immune response to an infection may be a factor in many cases. Approximately two-thirds of the cases of HSP occur days after symptoms of an upper respiratory tract infection develop.

Some causes of HSP have been linked to

1. vaccinations for typhoid, cholera, yellow fever, measles, or hepatitis B
2. foods
3. - Drugs
   4- Chemicals
   5- Insect bites.
4- Some experts also say that HSP is associated with the colder weather of fall and winter.
Diagnosis of Henoch-Schonlein Purpura

There is no specific test to diagnose HSP. It is diagnosed based on recognition of the classic symptoms, and exclusion of other conditions that can cause a similar rash. In many children with a classic rash, minimal testing is needed to establish a diagnosis of HSP. The rash is necessary for the diagnosis of HSP but is not always the first symptom to appear. When joint pain, swelling, or abdominal pain start before appearance of the rash, it can cause diagnosis can be challenging.

Tests in children with suspected HSP depend on the patient, but might include the following:

- **Platelet count** and coagulation studies to looks for other causes of bleeding.

- **Laboratory tests** to rule out other causes of vasculitis.

- **Evaluation of kidney function** by blood pressure check, creatinine level, electrolytes, and urine sample.

- In some patients, a **biopsy** may be taken of the skin, kidney or other tissue. Biopsies in patients with HSP often show **high levels of a specific type of immune protein, called immunoglobulin A (IgA)**.

- **Imaging of the bowels** may be performed if abdominal pain is severe.
Treatment of Henoch-Schönlein purpura

Most of the time, Henoch-Schönlein purpura improves on its own without treatment. Medical care is more likely to be needed if HSP involves the kidneys.

To help the children to feel better, the doctor may recommend medicines such as:

- antibiotics, if an infection is causing the HSP.
- pain relievers (such as acetaminophen).
- anti-inflammatory medicines (such as ibuprofen) to relieve joint pain and inflammation.
- corticosteroids (such as prednisone) for severe belly pain or kidney disease.
Respiratory disease

1. **Drug-Induced Pulmonary Disease**

Drug-induced pulmonary disease is lung disease brought on by a bad reaction to a medicine. Pulmonary means related to the lungs.

**What is the most common drug-induced respiratory problem?**

**Interstitial pneumonitis** (i.e., inflammation of the lung interstitium, such as the alveolar septa) is the most common manifestation of drug-induced lung disease.

**The Common Types of Drug-induced Pulmonary Diseases**

There are different types of lung or pulmonary diseases caused by drugs:

1. **Allergic reactions** like asthma, hypersensitivity pneumonitis, or eosinophilic pneumonia
2. **Lymph node swelling**
3. **Alveolar haemorrhage**, i.e., bleeding into lung sacs.
4. **Bronchitis**, i.e., inflammation of the airways.
5. **Pneumonia**
6. **Pulmonary edema**, i.e., fluid accumulation in the lungs.
7. **Pleural effusion** i.e., fluid accumulation around the lungs.
8. **Pulmonary fibrosis** i.e., formation of scar tissue in the lungs.
9. **Pulmonary arterial hypertension** i.e., defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise.
10. **Lung failure**.
Common Types of Drug-induced Pulmonary Diseases

- Bronchitis
- Pneumonia
- Pulmonary edema
- Pleural effusion
- Pulmonary Arterial Hypertension
Many medicines and substances are known to cause lung disease in some people. These include:

- Antibiotics, such as nitrofurantoin and sulfa drugs
- Heart medicines, such as amiodarone
- Chemotherapy drugs such as bleomycin, cyclophosphamide, and methotrexate
- Street drugs

**Symptoms**

Symptoms may include any of the following:

- Bloody sputum
- Chest pain
- Cough
- Fever
- Shortness of breath
- Wheezing
Diagnosis of Drug-induced Pulmonary Diseases

It has always been a challenge for pulmonologists to diagnose drug-induced pulmonary disease. The medications can cause reactions in varied forms, which makes it difficult for pulmonologists to identify the drug or its reaction. Tests that could detect changes in the lungs include the following:

1. **Imaging tests like chest x-ray and chest CT scan.**

2. **Lung function tests:** The primary purpose of pulmonary function testing is to identify the severity of pulmonary impairment. The tests measure lung volume, capacity, rates of flow, and gas exchange.

3. **Bronchoscopy:** is a procedure to look directly at the airways in the lungs using a thin, lighted tube (bronchoscope). The bronchoscope is put in the nose or mouth. It is moved down the throat and windpipe (trachea), and into the airways.

4. **Blood tests to rule out SLE-like reactions as a cause of the lung disease**

5. **Lung Biopsy, in rare cases**
2- Eosinophilic Pneumonia

Chronic eosinophilic pneumonia (CEP) is an idiopathic disorder characterized by an abnormal and marked accumulation of eosinophils in the interstitium and alveolar spaces of the lung causing inflammation and damage. Causes include smoking, allergic reactions and parasitic infections. EP may occur suddenly or worsen slowly.

What are the types of eosinophilic pneumonia?

There are three main types of eosinophilic pneumonia. They include:

- **Acute eosinophilic pneumonia**: This type worsens quickly as your blood oxygen level falls. Most patients with AEP completely recover with treatment.

- **Chronic eosinophilic pneumonia**: This type worsens slowly, over days or weeks. If untreated, it may persist over weeks or months and result in severe symptoms.

- **Löffler syndrome (simple pulmonary eosinophilic, or SPE)**: This form of eosinophilic pneumonia may cause no symptoms or only mild symptoms such as a dry cough. Löffler syndrome occurs due to a parasitic infection (roundworms). With treatment, the condition typically resolves within one month.
Causes of Eosinophilic pneumonia

Eosinophilic pneumonia has many causes, both infectious and noninfectious. But healthcare providers don't always know the exact cause.

**Common noninfectious triggers include:**

- Allergic reactions.
- Fungus (usually aspergillosis).
- Inhaled toxins, such as chemical fumes or particulate metals (found in the air) or dust.
- Medication, including commonly used antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs) or selective serotonin reuptake inhibitors (SSRIs).
- Smoking, especially if you've had a change in cigarette smoking habits (starting smoking for the first time or smoking more often).
- Underlying conditions, including cancer, autoimmune disease or inflammatory disease.
The symptoms of eosinophilic pneumonia

Signs of eosinophilic pneumonia vary, depending on the type and cause. Common symptoms include:

- Cough.
- Fever.
- Shortness of breath (dyspnea).

Acute eosinophilic pneumonia can worsen quickly, often within two weeks. Symptoms are usually more severe in people who smoke and may include:

- Chest pain.
- Chills.
- Fatigue.
- Muscle aches or muscle pain (myalgia).
- Without prompt diagnosis and treatment, the oxygen in your blood may fall to dangerously low levels. This can lead to acute respiratory failure in a few hours, requiring emergency treatment.

Common symptoms include:

- Shortness of breath that worsens.
- Night sweats.
- Unexplained weight loss.
- Wheezing.
Pathogenicity of Chronic Eosinophilic Pneumonia

The pathophysiological role of eosinophils in autoimmune diseases is not well defined; however, it has been shown that the production of pro-inflammatory cytokines stimulates and activates different cell groups, and can simultaneously induce autoantibodies and/or increased infiltration of eosinophils in various tissues, without an underlying autoimmune disease.

A proposed model for the pathogenesis of acute eosinophilic pneumonia. **IL-33** may be released by damaged epithelial cells responding to noxious stimulants such as allergens, infectious pathogens, and other inhalational toxins, including cigarette smoke. IL-33 and vascular endothelial growth factor (VEGF) may also be released by endothelial cells after drug-induced injury. In addition to IL-33, acute exposure to cigarette smoking induces epithelial cell release of IL-8, which mediates recruitment and activation of neutrophils. An additional source of IL-33 in the lung may be the activation of innate type 2 lymphoid cells, which have the capacity to rapidly generate IL-33 in response to certain stimuli. Subsequent generation and binding of IL-33 to cells expressing its receptor (ST2), including macrophages and dendritic cells, may lead to recruitment and activation of T-helper cell type 2 (Th2)-polarized T lymphocytes and production of cytokines like IL-5, which further promote recruitment and activation of eosinophils in the lung tissue. Eosinophils may also migrate into the lung because of chemokine gradients and increased permeability in the context of endothelial injury.
Diagnosed of Eosinophilic pneumonia

- medical history and travel.
- **physical exam**.
- Blood tests, including a **complete blood count**, to detect abnormalities.
- Broncho alveolar lavage (BAL) is the most important test to diagnose EP. Uses a flexible tube (**bronchoscope**) to collect fluid from your lungs to look for signs of disease.
- Chest x-ray and **CT scan**.
- Peripheral blood eosinophilia count, peripheral eosinophilia is often present in chronic eosinophilic pneumonia.
- Sedimentation rate (ESR)
The treatment for eosinophilic pneumonia

It may not treat a mild case of EP.

The three main types of eosinophilic pneumonia are treated with medications to control the underlying cause and its symptoms.

**Corticosteroids** to reduce swelling (inflammation) are the standard therapy and highly effective. In severe cases of AEP, providers may recommend other treatments to prevent respiratory failure:

- **Supplemental oxygen.**
- **Glucocorticoids (a type of corticosteroid).**

People with CEP often take steroids for an extended period, usually months. Some may require longer treatment.
Occupational lung diseases

Occupational or work-related lung diseases are lung conditions that have been caused or made worse by long-term exposure to certain irritants in the workplace. Dust particles, chemicals, fungal spores, and certain animal droppings are examples of exposures that may increase your risk of developing occupational lung disease.

There is no cure for occupational lung diseases. Controlling your exposure to lung irritants and treatment can help slow the disease progression, lessen symptoms, and improve your quality of life. If you smoke, quit. Smoking can cause or worsen lung disease.

The symptoms of an occupational lung disease
- Coughing
- Shortness of breath
- Chest pain
- Chest tightness
- Abnormal breathing pattern.

Types of occupational lung diseases
- Asthma.
- Bronchiolitis obliterans.
- COPD. (Chronic obstructive pulmonary disease)
- Hypersensitivity pneumonitis.
- Lung cancer.
- Mesothelioma.
- Pneumoconiosis.
The difference between inorganic and organic dust

**Inorganic** refers to any substances that do not contain carbon, excluding certain simple carbon oxides, such as carbon monoxide and carbon dioxide.

**Organic** refers to any substances that do contain carbon, excluding simple carbon oxides, sulfides, and metal carbonates.
Exposure to environmental and occupational lung irritants may put you at risk of developing chronic lung disease, including:

1. **Silicosis** is caused by breathing in tiny bits of silica, a mineral found in sand, quartz, and many other types of rock. Silicosis mainly affects workers exposed to silica dust in jobs such as construction and mining.

2. **Coccidioidomycosis or Valley fever** is an infection caused by breathing in the spores of the fungus Coccidioides found in the soil. Valley fever mainly affects workers exposed to dust storms or areas where contaminated soil is being disturbed, in jobs like construction or farming.

3. **Hypersensitive pneumonitis** is caused when you breathe in a specific substance (allergen) that triggers an allergic reaction in the body.

4. **Histoplasmosis** is caused by breathing fungal spores from soil that has been contaminated by bird or bat droppings. Some occupations that may expose workers to spores are farmers, pest control workers, poultry keepers, construction workers and landscapers.

5. **Asbestosis** is a naturally occurring mineral used as an insulation material and as a fire retardant. The main group at risk for asbestosis is people who worked in mining, milling, manufacturing, installation, or removal of asbestos products.
6. **Coal workers pneumoconiosis**, commonly known as black lung disease, occurs when coal dust is inhaled. Continued exposure to coal dust causes scarring in the lungs.

7. **Mesothelioma** is a rare type of cancer that occurs in the lining of the lungs and less commonly the lining of the abdomen. Asbestos exposure is the primary risk factor for mesothelioma. Occupations such as mining or milling, electricians, plumbers, pipe-fitters, insulators, or even remodelers of older homes still have a high risk of exposure.

8. **Work-related asthma**: Men working in forestry and minerals and women working in service industries (waitresses, cleaners, and dental workers) are most likely to develop occupational asthma.
Diagnose of an occupational lung disease

- **Pulmonary function tests**: diagnostic tests that help to measure the lungs' ability to move air into and out of the lungs effectively. The tests are usually performed with special machines into which the person must breathe.

- **Microscopic examination** from biopsy or autopsy of tissue, cells, and fluids from the lungs

- **Measurement of respiratory or gas exchange functions**

- **Examination of airway or bronchial activity**

How can occupational lung diseases be prevented?

The best prevention for occupational lung diseases is avoidance of the inhaled substances that cause lung diseases and Do not smoke. Smoking can actually increase the risk for occupational lung disease.
Clinical immunology

4th stage
Dr. Thabit Moath
Le No 20-19
Asthma

A chronic disease in which the bronchial airways in the lungs become narrowed and swollen, making it difficult to breathe. Symptoms include wheezing, coughing, tightness in the chest, shortness of breath, and rapid breathing. An asthma attack may be brought on by pet hair, dust, smoke, pollen, mold, exercise, cold air, or stress.

Asthma signs and symptoms include:

1. Shortness of breath
2. Chest tightness or pain
3. Wheezing when exhaling, which is a common sign of asthma in children
4. Trouble sleeping caused by shortness of breath, coughing or wheezing
5. Coughing or wheezing attacks that are worsened by a respiratory virus, such as a cold or the flu

Types of asthma

1. Allergic asthma
2. Seasonal asthma
3. Non allergic asthma
4. Exercise induced asthma
5. Difficult asthma
6. Childhood asthma
Causes

It isn't clear why some people get asthma and others don't, but it's probably due to a combination of environmental and inherited (genetic) factors. Exposure to various irritants and substances that trigger allergies (allergens) can trigger signs and symptoms of asthma. Asthma triggers are different from person to person and can include:

1. Airborne allergens, such as pollen, dust mites, mold spores, pet dander or particles of cockroach waste
2. Respiratory infections, such as the common cold
3. Physical activity
4. Cold air
5. Air pollutants and irritants, such as smoke
6. Certain medications, including beta blockers, aspirin, and nonsteroidal anti-inflammatory drugs, such as ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve)
7. Strong emotions and stress
8. Sulfites and preservatives added to some types of foods and beverages, including shrimp, dried fruit, processed potatoes.

Gastroesophageal reflux disease (GERD), a condition in which stomach acids back up into your throat
Pathophysiology

There are two phases of an asthma exacerbation, which include the early phase and late phase. The early phase is initiated by IgE antibodies that are sensitized and released by plasma cells. These antibodies respond to certain triggers in the environment, such as the risk factors listed above. IgE antibodies then bind to high-affinity mast cells and basophils. When a pollutant or risk factor gets inhaled, the mast cells release cytokines and eventually de-granulate. Released from mast cells are histamine, prostaglandins, and leukotrienes.
Simultaneously, cytokines derived from the mast cell will signal other inflammatory cells and their mediators to the lung. The result is airway inflammation, increased vascular permeability, mucus secretion, bronchospasm, and wheezing. These events are referred to as the early asthmatic response because they occur within minutes. A major component of the early response is bronchospasm. The late asthmatic response is delayed by hours. It is caused by a multitude of inflammatory cells continuing the inflammatory process. Of the inflammatory cells, the T cells play an important role. Antigen presenting cells may present a variety of allergenic antigens to chronically activated T helper cells. These cells then secrete multiple cytokines that maintain and intensify the local inflammatory response. Many other inflammatory cells, including mast cells and eosinophils, will respond to the T cells' cytokines. These inflammatory cells will produce cytokines, which amplify the cellular response and the inflammatory reaction. There is a migration of inflammatory cells from the circulation into the pulmonary vasculature and the airway submucosa. A central component to the inflammatory process as well as treatment is the arachidonic acid pathway, which leads to the generation of leukotrienes.
Pathogenesis of asthma

Antigen → Naive T-lymphocyte → Th-0 → IL-12→ Th-2 response

Th-1 response
(LIF-γ, lymphotoxin, IL-2)
→ Cell mediated immunity and Neutrophilic inflammation

Th-2 response
(IL-4, IL-13, IL-9, IL-4, IL-3, GM-CSF)
→ IgE → Mast cells → Basophils → Eosinophils

Mediators of inflammation (e.g., histamine, prostaglandins, leukotrienes, enzymes)

Asthma symptoms → Bronchial hyperresponsiveness → Airway obstruction
Diagnosis

Lung function tests:- These are also called (pulmonary function tests.) Lung function tests detect how well you inhale (breathe in) and exhale (breathe out) air from your lungs. These tests measure breathing.

Lung function tests are often done before and after inhaling a medication known as a bronchodilator. This medicine opens the airways. If lung function improves a lot with a bronchodilator, the patient likely has asthma.

**Common Lung function tests used to assess airways include:**

a. **Spirometry**: A type of lung function test that measures how much you breathe in and out and how fast you breathe out.

b. **FeNO test (exhaled nitric oxide)**: A test that helps assess inflammation in the airways.

c. **Bronchial provocation or “trigger” tests**: Tests that measure if lungs are sensitive to certain irritants or triggers such as methacholine or histamine.

d. **Diffusion Capacity**: Diffusion capacity measures how well oxygen flows from the lungs into your blood. Poor diffusion indicates damage to the lung where the oxygen and blood meet in the lungs. Diffusion capacity is usually normal in asthmatics.
3- **Allergy tests**

4- **Blood tests:** measured the levels of immunoglobulin E (IgE) and Eosinophil. If the levels are high, this could be a sign of severe asthma.

5- **Chest X-Ray:** in asthma, the chest X-ray is likely to show air trapping or hyper-expansion.

**Treatment of asthma**

- **Bronchodilators:** These medicines relax the muscles around your airways. The relaxed muscles let the airways move air. They also let mucus move more easily through the airways. These medicines relieve your symptoms when they happen and are used for intermittent and chronic asthma.

- **Anti-inflammatory medicines:** These medicines reduce swelling and mucus production in your airways. They make it easier for air to enter and exit your lungs.

- **Biologic therapies for asthma:** These are used for severe asthma when symptoms persist despite proper inhaler therapy.
5- Non-allergic bronchitis

It is a form of lower respiratory tract infection occurs due to a **viral or bacterial infection**. Some people develop non-allergic bronchitis after a cold, for instance. Bronchitis can be **acute or chronic**. Acute form leads to **cough**, which may **contain mucus**, while in case of chronic bronchitis, **cough last for more than a few months**. Air pollution and smoking are some major causes of bronchitis.

**Symptoms of Acute Bronchitis**

Each person is different, and symptoms will vary depending on the cause of inflammation. The symptoms associated with acute bronchitis are similar to those of the **cold and flu** and last less than **3 weeks**.

- Coughing with or without mucus
- A runny nose
- A sore throat
- Sneezing
- Fever & chills
- Breathing difficulties
- Extreme fatigue
- Mild headache
- Mild body ache
A

- Trachea
- Bronchus
- Right lung
- Left lung

B

- Bronchial wall
- Bronchus lined with a thin layer of mucus

C

- Inflamed bronchial wall
- Bronchus with increased amount of mucus
Causes

A virus usually causes acute bronchitis. Bacteria can sometimes cause acute bronchitis. But, even in these cases, taking antibiotics is NOT advised and will not help you get better.

Diagnosis

1. **Spirometry** :- A test that measures lung function as breathe in and out of a mouthpiece that is attached to a device called a spirometer.
2. **Peak expiratory flow** :- A test that measures the force of air breathe out (exhale) into the mouthpiece of a device called a peak expiratory flow meter
3. **Chest X-ray** :- A radiology test that produces images of the chest to look for evidence of other conditions that could be causing your cough and breathing problems.
4. **Complete blood count (CBC) with differential**
5. **Procalcitonin levels** (to distinguish bacterial from nonbacterial infections)
6. **Sputum cytology** (if the cough is persistent)
7. **Blood culture** (if bacterial superinfection is suspected)
8. **Chest radiography** (if the patient is elderly or physical findings suggest pneumonia)
9. **Bronchoscopy** (to exclude foreign body aspiration, tuberculosis, tumors, and other chronic diseases)
10. **Influenza tests**
11. **Laryngoscopy** (to exclude epiglottitis)
Treatment

Treatment of acute bronchitis is typically divided into two categories: antibiotic therapy and symptom management.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 22-21
Tumors and Tumor Markers

Tumor Immunology

The proliferation of normal cells is carefully regulated. However, such cells when exposed to chemical carcinogens, irradiation and certain viruses may undergo mutations leading to their transformation into cells that are capable of uncontrolled growth, producing a tumor or neoplasm.

The tumor may be:

- Benign, if it is not capable of indefinite growth and the host survives.
- Malignant, if the tumor continues to grow indefinitely and spreads (metastases). This uncontrolled growth may be due to up regulation of oncogenes (cancer-inducing genes) and/or down regulation of tumor suppressor genes (that normally inhibit tumor growth often by inducing cell death).
Tumor associated antigens

There are 2 main types of tumor antigens:

- Tumor-specific transplantation antigens (TSTA) which are unique to tumor cells and not expressed on normal cells.
- Tumor associated transplantation antigens (TATA) that are expressed by tumor cells and normal cells.

Tumor-associated developmental antigens or onco-fetal antigens:-

These include alpha-fetoprotein (AFP) and carcino-embryonic antigen (CEA) found secreted in the serum. AFP is found in patients with hepatocellular carcinoma whereas CEA is found in colon cancer. These are important in diagnosis. AFP is produced only as a secreted protein whereas CEA is found both on cell membranes and in secreted fluids.
Viruses that cause human tumors include:

**DNA viruses**

- Papova (papilloma, polyoma) viruses: Papilloma virus causes cervical cancer.
- Hepatitis virus: Hepatitis B virus causes hepatocellular cancer.
- Adenoviruses may also be tumorigenic
- Certain types of Herpes Virus (CMV and EBV)

**RNA viruses**

- Retroviruses: Human T-lymphotropic viruses (HTLV-I and HTLV-II) causes T-cell leukemias.
Immunity against Tumor: There is several anti-tumor immune reactivity in human;

1. **Cell-mediated immunity** plays a critical role in **tumor rejection**.

2. The **T helper (Th)** cells recognize the tumor antigens that may be shed from tumors and internalized, processed and presented in association with class II MHC on antigen presenting cells. These Th cells, will produce cytokines, provide help to B cells in antibody production.

3. Cytokines such as **IFN-gamma γ** may also activate **macrophages** to be tumoricidal.

4. The Th cells also provide help to **tumor-specific cytotoxic T cells (CTLs) CD8**\(^+\) and **NK cell** by inducing their proliferation and differentiation.

5. The **CTLs** recognize **tumor antigens** in the context of class I MHC and mediate tumor cell lysis.

6. In tumors with decreased MHC antigens, **natural killer (NK) cells** are important in mediating tumor rejection.
Immune Response to Tumours

- The immune response to tumors includes
  - CTL-mediated lysis,
  - NK-cell activity,
  - macrophage-mediated tumor destruction, and
  - destruction mediated by ADCC.

Taradi
Tumor Marker (TM):-

T.M or also known as biomarkers are indicators of cellular, biochemical, molecular, or genetic alterations by which neoplasia can be recognized. It is measurable biochemical that are associated with a malignancy, they are substances found at higher than normal levels in some peoples with cancer.

Classification:- The T.M. is either produced by the tumor cells (tumor derived) or by the body in response to tumor cells (Tumor associated).

1. **Tumor Specific Antigens**: - Present on tumor cells and not on any normal cells.
2. **Tumor Associated Antigens**: - Are present on tumor cells and also on some normal cells in response to the tumor.
Clinically associated useful of TMs:

- Diagnostic and distinguish benign from malignant disease
- Correlate with the amount of tumor present (so-called tumor burden)
- Allow subtype classification to more accurately stage patients
- Be prognostic, either by the presence or absence of the marker or by its concentration
- Guide choice of therapy and predict response to therapy
Type of T.Ms. (specific and /or sensitive)

As like other laboratory Testing, T.Ms. test must be both specific and sensitive.

Specificity: - If either the T.Ms. it self or the test used to detect or measure it is not specific enough, there is a chance that the results could suggest a tumor is presents, or growing despite treatment, when it is not (a false positive). High specificity – not present in other diseases, non-tumors and in healthy subjects

Sensitivity: - If the T.Ms. or the test is not sensitive enough, the result may suggest a tumor is not present when it actually is or that is responding to treatment, when it is not (A false Negative). High sensitivity – detectable at the beginning of the disease
Main Examples of T.Ms. in cancers:

Protein Tumor Markers:
- Carcinoembryonic antigen (CEA)
- α-Fetoprotein (AFP).
- Carbohydrate Antigen (CA 19-9). (CA 125). monitoring of ovarian CA
- Prostate-Specific Antigen (PSA).
- CA 15-3 – monitoring of breast CA
- CA 72 CA 72-4– monitoring of gastric CA
- CA 19 CA 19-9 9 for monitoring of pancreas CA (and bile ducts)
- Human Chorionic Gonadotropin in Testicular Germ Cell Tumors
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 23-24
Hypersensitivity (also called hypersensitivity reaction or intolerance) is a set of 
undesirable reactions produced by the normal immune system, including allergies and 
autoimmunity. They are usually referred to as an over- reaction of the immune system and 
these reactions may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity 
reactions require a pre-sensitized (immune) state of the host. They are classified in four 
groups after the proposal of P. G. H. Gell and Robin Coombs in 1963.

**Type I:** IgE mediated immediate reaction

**Type II:** Antibody-mediated reaction (IgG or IgM antibodies)

**Type III:** Immune complex-mediated reaction

**Type IV:** Cytotoxic, cell-mediated, delayed hypersensitivity reaction
**Type I**

- **IgE-Mediated Hypersensitivity**
- IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.
- Causes localized and systemic anaphylaxis. Seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema.
Type II

- IgG-Mediated Cytotoxic Hypersensitivity

- Cells are destroyed by bound antibody, either by activation at complement or by a cytotoxic T cell with an Fc receptor for the antibody {ADCC}

- Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis
Immune Complex-Mediated Hypersensitivity

Antigen-antibody complexes are deposited in tissues, causing activation at complement, which attracts neutrophils to the site.

- Most common forms at immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and endemic lupus erythematosus.
• Cell-Mediated Hypersensitivity

• Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site

• Most common terms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis
**Type I - IgE-Mediated Hypersensitivity**

IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation. IgE is involved in the hypersensitivity type I and can cause localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema.

**Type II - IgG-Mediated Cytotoxic Hypersensitivity**

Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC). Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis.

**Type III - Immune Complex-Mediated Hypersensitivity**

Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site. Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.

**Type IV - Cell-Mediated Hypersensitivity**

Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site. Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis.

**Antigen-Dependent Cellular Cytotoxicity**

- **Cytotoxic T cell**
- **Fc receptor for IgG**
- **Surface antigen**
- **Target cell**

**Complement Activation**

- **Neutrophil**
- **Surface antigen**

**Free-floating immune complex**

- **Cytotoxic T cell**
- **Sensitized Th1 cell**

**Activated macrophage**

- **Cytotoxic T cell**
- **Cytokines**
The antigen-specific IgE antibodies can then bind to high-affinity receptors located on the surfaces of mast cells and basophils. Reexposure to the antigen can then result in the antigen binding to and cross-linking the bound IgE antibodies on the mast cells and basophils. This causes the release and formation of chemical mediators from these cells.

The major mediators and their functions are described as follows:

1. **Histamine**: This mediator acts on histamine 1 (H1) and histamine 2 (H2) receptors to cause contraction of smooth muscles of the airway and GI tract, increased vasopermeability and vasodilation, enhanced mucus production, pruritus, cutaneous vasodilation, and gastric acid secretion.

1. **Tryptase**: Tryptase is a major protease released by mast cells. Its role is not completely understood, but it can cleave C3, C3a, and C5 in addition to playing a role in airway remodeling. Tryptase is found in all human mast cells but in few other cells and thus is a good marker of mast cell activation.

1. **Proteoglycans**: Proteoglycans include heparin and chondroitin sulfate. The role of the latter is unknown; heparin seems to be important in storing the preformed proteases and may play a role in the production of alpha-tryptase.

1. **Chemotactic factors**: An eosinophilic chemotactic factor of anaphylaxis causes eosinophil chemotaxis; an inflammatory factor of anaphylaxis results in neutrophil chemotaxis. Eosinophils release major basic protein and, together with the activity of neutrophils, can cause significant tissue damage in the later phases of allergic reactions.
Diagnosis of hypersensitivity

Laboratory testing may include:

1- Allergen-specific IgE blood testing: this is testing that is used to help diagnose allergies. The test measures the amount of allergen-specific IgE antibodies in the blood in order to detect an allergy to a particular substance.

The RAST (Radioallergosorbent test) is a laboratory test performed on blood. It tests for the amount of specific IgE antibodies in the blood which are present if there is a "true" allergic reaction.

Note: The traditional method for blood testing was the RAST (radioallergosorbent test), but it has been largely replaced with newer IgE-specific immunoassay methods. Some health practitioners, however, still refer to all IgE allergy blood tests as RAST even though it is not the methodology that the laboratory uses.
Other types of allergy tests:

1. **Skin prick or scratch tests** are done in an allergist's or dermatologist's office and must be done by a trained professional. They are often used to detect airborne allergies such as pollens, dust, and molds. Because of the potential for a severe reaction, skin prick tests are not usually used for food allergies. The person being tested must not have significant eczema or be taking antihistamines or certain antidepressants for several days before the skin prick test. False positives can arise with even a non-allergic person if the dosage of the allergen is high enough.
Intradermal allergy skin tests, using injections that form a bubble under the skin, may be done but they are not widely accepted because of a high false-positive rate.
**Patch testing:**- Delayed hypersensitivity skin and patch tests are the easiest methods of testing for type IV delayed hypersensitivity. A concentration of the suspected allergen is applied to the skin under a nonabsorbent adhesive patch and left for 48 hours. If burning or itching develops more rapidly, the patch is removed. A positive test consists of redness with some hardening and swelling of the skin and sometimes vesicle (blister-like) formation. Some reactions will not appear until after the patches are removed, so the test sites are also checked at 72 and 96 hours.
4. Oral food challenges are considered the "gold standard" for diagnosing food allergies. They are labor-intensive and require close medical supervision because reactions can be severe, including life-threatening anaphylaxis. Food challenges involve giving a person small amounts of unmarked potential food allergens in capsule or intravenous form and watching for allergic reactions. Negatives are confirmed with larger meal-sized portions of food.
4. **Food elimination** is another way to test for food allergies: eliminating all suspected foods from the diet, then reintroducing them one at a time to find out which one(s) are causing the problem.

2- **Total IgE testing** is sometimes done to look for an ongoing allergic process. It is a blood test that detects the total amount of IgE protein (including allergy antibodies) but does not identify specific allergens. Conditions besides allergies can also cause the IgE level to rise.

3- **Complete blood count (CBC) and WBC differential**—these tests include the measurement of eosinophils, a type of white blood cell. The level of eosinophils may be increased in a person with allergies.

4- **Histamine and/or tryptase blood tests** may be used to help diagnose anaphylaxis or mast cell activation.
4. The MELISA® test (Memory Lymphocyte Immuno Stimulation Assay) measures hypersensitivity to numerous metals, including mercury, by placing a series of metals into contact with the white blood cells of the person being tested and then monitoring the reaction. An innovative diagnostic tool.
Treatment

The treatment of immediate hypersensitivity reactions includes the management of anaphylaxis with intramuscular adrenaline (epinephrine), oxygen, intravenous (IV) antihistamines, support blood pressure with IV fluids, avoid latex gloves and equipment in patients who are allergic, and surgical procedures such as tracheotomy if there is severe laryngeal edema.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 25-26
Immunological Thyroid Disease
AITD are the more frequent pathological conditions of the thyroid gland. Although appearing as a single pathologic entity, the AITD comprise two main clinical presentations: Graves’ disease and Hashimoto’s thyroiditis. Both conditions are characterized by lymphocytic infiltration of the thyroid parenchyma.

In Graves’ disease, the infiltration is mild and induces the production of anti-TSH receptor antibodies that stimulate the growth and the function of thyroid follicular cells, ultimately leading to hyperthyroidism.

In Hashimoto’s thyroiditis, the lymphocytic infiltration is more severe and causes the destruction of the thyroid follicles and subsequent hypothyroidism. It is a typical T cell-mediated autoimmune disease, characterized by the ectopic formation of tertiary lymphoid follicles within the thyroid gland.
Causes of autoimmune thyroid diseases

1. Genetic susceptibility

2. Environmental factors

Aside the genetic factors, the remaining 20% or so contribution to the occurrence of AITD is thought to be due to environmental factors. Several factors have been identified and proposed. These include radiation, iodine status, smoking, infection, stress and drugs such as lithium and interferon.

3. Radiation

External radiation for Hodgkin’s disease triggers the subsequent occurrence of antithyroid antibodies and AITD, hypothyroid thyroiditis as well as Graves’ disease. Similarly, radioiodine treatment of toxic goitre may be followed, years later, by the occurrence of Graves’ disease, even Graves’ ophthalmopathy. In a different context, children exposed to radiation from Chernobyl showed a greater incidence of thyroid autoantibody positivity, with no increase in the incidence of hypothyroidism.
4. **Stress:** As early as one of the first description of the disease, stress has been considered as a trigger factor for Graves’ disease onset. An abundant literature is devoted to that question, the approach of which remains relatively uncertain in the absence of objective markers.

5. **Drugs:** **Lithium treatment** is associated with an increased prevalence of thyroid antibodies, hypothyroidism and, to a lesser extent, of Graves’ disease. However, lithium-induced AITD must be differentiated from the inhibitory effect of lithium on thyroid secretion. **Interferon**-induced thyroiditis can manifest as classical autoimmune thyroiditis or, rarely, Graves’ disease, but also as non-autoimmune thyroiditis. **Whether the hepatitis C virus** itself plays a role in the disease remains questionable.
Symptoms

The symptoms may vary depending on the thyroid function, i.e. [hyperthyroidism](#) or [hypothyroidism](#).

**Hyperthyroidism** can cause sweating, rapid heart rate, anxiety, tremors, fatigue, difficulty sleeping, sudden weight loss, and protruding eyes.

**Hypothyroidism** can cause weight gain, fatigue, dry skin, hair loss, intolerance to cold, and constipation. The effects of this disease may be permanent but can sometimes be transient.
Symptoms may come and go depending on whether the person receives treatment.

1. Tiredness
2. Sensitivity to cold
3. Puffy face
4. Trouble pooping
5. Enlarged tongue
6. Pale, dry skin and brittle nails
7. Hair loss
8. Weight gain
9. Muscle aches and joint pain
10. Depression
11. Memory lapse
12. Heavy menstrual bleeding
Pathogenesis of AITD

Thyroid autoantibodies appear mostly with the presence of lymphocytes in the targeted organ. Lymphocytes produce antibodies targeting three different thyroid proteins: Thyroid peroxidase Antibodies (TPOAb), Thyroglobulin Antibodies (TgAb), and Thyroid stimulating hormone receptor Antibodies (TRAb). Some patients who are healthy may be positive for more than one of these antibodies. Doctors who attend to such patients will most likely do routine follow-ups on the patient’s health since, even though it is highly unlikely that they will present any thyroid problems, there is still a chance that they will develop some type of dysfunction with time.

AITD is characterized by lymphocytic infiltration in the thyroid gland and the production of pathogenic thyroid autoantibodies. Autoantibodies against various thyroid antigens such as thyroid peroxidase (TPO), Tg, sodium iodide symporter, and pendrin are detected in the sera from patients with Hashimoto's thyroiditis. Production of TSAb against TSHR result is Graves' hyperthyroidism. It is clear that the production of autoantibodies requires disruption of self-tolerance and an adaptive immune response.
For thyroid function evaluation, thyrotropin (TSH) is the usual starting point. TSH shows an exponential response to changing peripheral thyroid hormone levels, thereby providing high clinical detection sensitivity.

Thyroxine (T4) or triiodothyronine (T3) is frequently measured alongside, mostly as free hormones (FT4 and FT3), to assess disease severity or treatment response. Some diseases require additional testing to determine the cause of observed abnormalities or to clarify contradictory results of TSH and T4/T3 testing. Thyroid autoantibody testing is important in this context.

Testing for structural thyroid disease centers on tumor markers, mainly thyroglobulin (Tg), calcitonin, and carcinoembryonic antigen, all of which are primarily used for follow-up.
Various tests can be chosen depending on the presenting symptoms. Doctors may search for Thyroid peroxidase Antibodies (TPOAb) when a person has symptoms of hypothyroidism, or when a person will be started on a drug therapy associated with risks of developing hypothyroidism, such as lithium or Interferon alfa. This antibody is related to Hashimoto's thyroiditis and Graves' disease. If the person presents symptoms of hyperthyroidism, doctors are more likely to test for Thyroid stimulating hormone receptor Antibodies (TRAb), and monitor the effects of anti-thyroid therapy, also associated with Graves' disease.

Doctors may check Thyroglobulin Antibodies (TgAb) also, whenever a thyroglobulin test is performed to see if the antibody is interfering. TgAb may also be ordered in regular intervals after a person has been diagnosed with thyroid cancer, and just like TPOAb, it can be associated with Hashimoto’s thyroiditis.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 27-28
Autoimmune Hemolytic Anemia

Autoimmune [hemolytic anemia](autoimmune-hemolytic-anemia) (or autoimmune haemolytic anaemia; AIHA) occurs when [antibodies](antibodies) directed against the person's own [red blood cells](red-blood-cells) (RBCs) cause them to [burst](burst) (lyse), leading to an insufficient number of oxygen-carrying red blood cells in the circulation. The lifetime of the RBCs is reduced from the normal 100–120 days to just a few days in serious cases. The [intracellular components](intracellular-components) of the RBCs are released into the [circulating blood and into tissues](circulating-blood-and-into-tissues), leading to some of the characteristic symptoms of this condition. The antibodies are usually directed against high-incidence [antigens](antigens), therefore they also commonly act on allogenic RBCs (RBCs originating from outside the person themselves, e.g. in the case of a blood transfusion). AIHA is a relatively rare condition, affecting one to three people per 100,000 per year.

Autoimmune hemolytic anemia is a group of disorders characterized by a malfunction of the immune system that produces autoantibodies, which attack red blood cells as if they were substances foreign to the body.
Types :- There are two classifications for AIHA:

1. **warm and cold** (The classification depends on the type of antibodies involved.)

2. a. **Primary AIHA** is when there is no sign of any underlying condition.
   b. **Secondary AIHA** is when there is a link with another condition.
Warm AIHA

Also called warm hemolysis, this involves IgG antibodies. These bind red blood cells at 98.6°F (37°C), or normal body temperature. This accounts for 80–90 percent of cases.

Cold AIHA

This is also called cold hemolysis. In this type, IgM autoantibodies, or cold agglutinins, bind red blood cells when the blood is exposed to cold temperatures, specifically 32° to 39.2°F (0° to 4°C). This accounts for 10–20 percent of cases.

Symptoms :- Common symptoms of AIHA include:

- a low-grade fever
- weakness and tiredness
- difficulty thinking and concentrating
- paleness
- rapid heartbeat
- shortness of breath
- up
- yellowing skin, or jaundice
- dark urine
- muscle pains
- headaches
- nausea, vomiting, and diarrhea
- lightheadedness when standing
- difficulty breathing
- a sore tongue
- heart palpitations or a rapid heartbeat
Diagnosis

1. Complete blood count

2-Coombs tests: These blood tests look for antibodies that may affect the red blood cells.
Positive: A clumping of the red blood cells (agglutination) during the test.
Agglutination of blood cells during a direct Coomb’s test suggests that antibodies may be present on red blood cells of the patient and that the condition of hemolysis may persist.
Agglutination of blood cells during an indirect Coomb’s test suggest the presence of antibodies circulating in bloodstream that could cause the immune system to react to any red blood cells that are considered foreign to the body — particularly those that may be present during a blood transfusion.
- Reticulocyte test

This blood test measures the levels of reticulocytes, which are slightly immature red blood cells. It can determine whether the bone marrow is creating red blood cells at a suitable rate.

The range will be higher if the body has low hemoglobin levels due to bleeding or red cell destruction. High red blood cells production can be a sign of anemia.

4- Bilirubin test

The liver produces bilirubin, a yellow-colored substance that is present in bile. A blood test can measure the amount of bilirubin in the blood. When blood cells die, hemoglobin enters the bloodstream. Hemoglobin, in turn, breaks down into bilirubin. This leads to jaundice, when the eyes and skin take on a yellowish color. High bilirubin levels in the blood can be a sign of anemia, liver damage, or another disease.
Haptoglobin test

Haptoglobin is a protein that the liver produces. Within the body, it connects a specific type of hemoglobin within the blood. The amount of haptoglobin in the blood shows how fast red blood cells are being destroyed.

Treatment

Treatment options for AIHA depend on a number of factors. If the anemia is mild, it often passes without treatment. Between 70 and 80 percent of people need no treatment or minimal intervention.

1. Corticosteroids is the first type of treatment for people with primary AIHA, and it can help to improve symptoms in many common types of AIHA.

2. Immunosuppressive therapy in severe cases.

1. Surgery: The spleen is responsible for removing abnormal red blood cells from the bloodstream, including those with antibodies attached. Removing the spleen can enable the body to preserve those red blood cells. This can help to prevent anemia.

2. Blood transfusion
ECZEMA & CONTACT DERMATITIS

eczema, is a group of diseases that results in inflammation of the skin. These diseases are characterized by itchiness, red skin, and a rash. In cases of short duration there may be small blisters while in long-term cases the skin may become thickened. The area of skin involved can vary from small to the entire body.

Dermatitis is a group of skin conditions that includes atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, and stasis dermatitis. The exact cause of dermatitis is often unclear. Cases may involve a combination of irritation, allergy, and poor venous return.
Classification:

A. Exogenous eczemas – are related to clearly defined external triggering factors, although inherited tendencies can also play a part, this group include:

1. Irritant contact dermatitis (ICD).
2. Allergic contact dermatitis (ACD).
3. Photo-contact dermatitis.
4. Infective dermatitis.
5. Dermatophytide.

B.
- **Endogenous eczema** – It implies that the condition is not a result of exogenous or external environmental factors, i.e. is mediated by **processes originating within the body**, include:

  1. **Atopic dermatitis (AD)**.
  2. **Hand eczema and pompholyx**.
     - الفاقوع خلل التعرق (Dyshidrosis)، والذي يعرف أيضاً ب إكزيما خلل التعرق (dyshidrotic eczema)، أو (pompholyx) (blisters) أو ينير على الكفين أو باطن القدمين، وتبقى هذه البثور عادة ما يقارب 3-4 أسابيع، وتسبب حكة شديدة وألم وشفان في الجلد.
  3. **Asteatotic eczema**.
  4. **Discoid eczema**.
  5. **Exudative discoid and lichenoid dermatitis**.
  6. **Chronic superficial scaly dermatitis**.
  7. **Pityriasis alba**.

الاكزيما الذهبية
الاكزيما القرصية
الالتهاب الجلدي النضحي القرصي
الاكزيما القشرية
النخالية
Symptoms

Although every type of dermatitis has different symptoms, there are certain signs that are common for all of them, including:

1. Redness of the skin,
2. Swelling,
3. Itching and skin lesions.
4. Sometimes oozing and scarring.
5. Typical affected skin areas include the folds of the arms, the back of the knees, wrists, الرسغين face and hands.
Causes :-
The cause of eczema is unknown but is presumed to be a combination of genetic and environmental factors.

1-Environmental :- The hygiene hypothesis postulates that the cause of asthma, eczema, and other allergic diseases is an unusually clean environment.

2-Genetic :- A number of genes have been associated with eczema, Eczema occurs about three times more frequently in individuals with celiac disease.
Pathophysiology

The pathophysiology of atopic dermatitis is complex and multifactorial, involving elements of barrier dysfunction, alterations in cell mediated immune responses, IgE mediated hypersensitivity, and environmental factors. The imbalance of Th2 to Th1 cytokines observed in atopic dermatitis can create alterations in the cell mediated immune responses and can promote IgE mediated hypersensitivity, both of which appear to play a role in the development of atopic dermatitis. One must additionally take into consideration the role of the environment on the causation of atopic dermatitis and the impact of chemicals such as airborne formaldehyde, harsh detergents, fragrances, and preservatives. Use of harsh alkaline detergents in skin care products may also unfavorably alter the skin’s pH causing downstream changes in enzyme activity and triggering inflammation. Environmental pollutants can trigger responses from both the innate and adaptive immune pathways.
Diagnosis

Diagnosis of eczema is based mostly on the history and physical examination. However, in uncertain cases, skin biopsy may be useful. Those with eczema may be especially prone to misdiagnosis of food allergies. Patch tests are used in the diagnosis of allergic contact dermatitis.

An atopy patch test can be used to determine whether or not a specific allergen is the cause of the rash. The test involves applying a series of allergens to the skin surface and evaluating the results in one to three days.

A patch test is a method used to determine whether a specific substance causes allergic inflammation of a patient's skin. Any individual suspected of having allergic contact dermatitis or atopic dermatitis needs patch testing.
Medications

- **Medicated products applied to the skin.** Many options are available to help control itching and repair the skin. Products are available in various strengths and as creams, gels and ointments.

**Drugs to fight infection :-** Antibiotics are used to treat the infection.

- **Pills that control inflammation.** Options might include cyclosporine, methotrexate, prednisone, mycophenolate and azathioprine. These pills are effective but can't be used long term because of potential serious side effects.

- **Other options for severe eczema.** The injectable biologics (monoclonal antibodies) dupilumab (Dupixent) and tralokinumab (Adbry) might be options for people with moderate to severe disease who don't respond well to other treatment.
Clinical immunology

4th stage

Dr. Thabit Moath

Le No 29-30
Immunology of transplantation

Graft or Transplant: Transfer of living cells, tissues and organs from one part of the body to another or from one individual to another.

The transplantation mainly based on:

1. Organ or tissue transplanted
2. Anatomical site of origin of transplant & site of its placement:
   a. Orthotopic: normal sites
   b. Heterotopic: abnormal sites
1. Genetic compatibility and antigenic relationship.
2. Fresh or stored transplanted tissue:

Types of Transplantation:-

1. Autologous.
2. Syngeneic.
3. Allogenic.
4. Xenogeneic.
Auto grafting (Autologous) -

Transfer of self-tissue from one body site to another in the same individual, it should:
Genetic homology of the tissue-immune system does not respond (Skin, hair grafts). Auto graft acceptance epidermis:

1. After 3-7 days have revascularization of blood vesicles.
2. 7 – 10 days healing.
3. 12 -14 neutrophil resolution,

Allograft reaction:-

First Set Response :- Skin graft from a genetically unrelated animal of same species. Initial acceptance, Thrombosed and necrosed Mainly by T lymphocytes.
- After 3-7 days have revascularization of blood vesicles.
- 7 – 10 cellular infiltration,
- 10 -14 thromboses and necrosis,
- > 14 day damaged blood vesicles and rejection the implanted tissues.
(a) Autograft acceptance
Grafted epidermis
Blood vessels
Days 3–7: Revascularization

(b) First-set rejection
Grafted epidermis
Blood vessels
Days 3–7: Revascularization

Days 7–10: Healing
Neutrophils

Days 7–10: Cellular infiltration
Blood clots

Days 12–14: Resolution

Days 10–14: Thrombosis and necrosis
Damaged blood vessels
Second Set Response :- If an animal has rejected a graft by the first set response, another graft from the same donor is applied – rejected in an accelerated manner, Mainly by antibodies

Effecter mechanism of allograft rejection:-

- Hyper acute Rejection
  a. Pre-existing specific antibodies in high titers in the host circulation bind to donor endothelial antigens.
  b. Activates Complement Cascade.
  c. Characterized by thrombotic occlusion of graft
  d. Graft remains pale
  e. Rejected within minutes or hours, even without an attempt at vascularization
Hyperacute Rejection

1. Preformed Ab, 2. complement activation,
3. neutrophil margination, 4. inflammation,
5. Thrombosis formation
Immunological Enhancement: -

Humoral antibodies can act in opposition to CMI by inhibiting graft rejection.

- **Afferent inhibition**: Combine with antigens released from graft so that they are unable to initiate an immune response.

- **Central inhibition**: Antibodies may combine with lymphoid cell, by a negative feedback, render them incapable of responding to the antigens of the graft.

- **Efferent inhibition**: By coating the surface of cells in the graft so that sensitized lymphocytes are kept out of contact with them.

Acute Rejection: -

- Vascular and parenchymal injury mediated by T cells and antibodies that usually begin after first week of transplantation if no immunosuppressant therapy.

- Incidence is high (30%) for the first 90 days.
Acute Rejection

T-cell, macrophage and Ab mediated, myocyte and endothelial damage, Inflammation
Chronic Rejection :-
- Occurs in most solid organ transplants
- Heart, Kidney, Lung, Liver
- Characterized by :
  a. Fibrosis
  b. Vascular abnormalities
  c. Loss of graft function over a prolonged period.
Macrophage - T cell mediated
Concentric medial hyperplasia
Chronic DTH reaction
Histocompatibility antigens.

Antigens that participate in graft rejection are called transplantation or histocompatibility antigens:

- ABO blood group
- HLA system (MHC restricted allograft Rejection)

Histocompatibility Testing: -

- ABO blood grouping
- HLA compatibility:
- Tested by HLA typing and tissue matching
- HLA typing identifies the HLA antigens expressed on the surface of leucocytes

Methods of HLA – Typing: -

- Microcytotoxicity test.
- Molecular methods
  a. PCR using sequence specific primers.
- Tissue matching.
Can be employed to approximate the risk of a given recipient of having a positive crossmatch. This is to a likely organ donor taken from a similar population.

**Figure 1**

Schematic diagram of lymphocyte based antibody screening and solid phase (bead based) antibody screening. A: Cell based antibody screening; B: Solid phase (bead based) antibody screening.
Micro Cytotoxicity: -

Tests for complement mediated lysis of peripheral blood lymphocytes with a standard set of typing sera. Micro-cytotoxicity assay, utilizes serum with known anti-HLA antibodies that recognize particular HLA loci (HLA-A, HLA-B, HLA-C, HLA-DQ, HLA-DR /not DP) in order to match genetically similar individuals in hopes of performing a tissue transplantation.

Graft-versus-host (GVH) reaction: -

Graft rejection is due to the reaction of the host to the grafted tissue, Host-versus-graft response , The contrary situation, in which the graft mounts an immune response against the antigens of the host, is known as: Graft-versus-host (GVH) reaction.

Essential Component Required for (GVH)

The GVH reaction occurs when the following conditions are present:

1. The graft contains immunocompetent T cells.
2. The recipient possesses transplantation antigens that are absent in the graft.
3. The recipient must not reject the graft.
When grafted tissue has mature T cells, they will attack host tissue leading to GVHR. Major problem for bone marrow transplant.

**Methods to overcome GVHR:**
- Treat bone marrow to deplete T cells.
- Use autologous bone marrow.
- Use umbilical cord blood.

Caused by the reaction of grafted mature T cells in the marrow inoculum with alloantigens of the host

- **Acute GVHD:** Characterized by epithelial cell death in the skin, GI tract, and liver.
- **Chronic GVHD:** Characterized by atrophy and fibrosis of one or more of these same target organs as well as the lungs.