

# The immune system, immunopathology. Infectious diseases

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# Physiologic function

## **Protection + defence against external and/or internal noxae**

- Defence against infection incl. toxic products
- Autotolerance against body-own antigenes
- Immunologic internal control (removal of old, defective, some mutated cells)

Failure possible due to inadequate immune function and/or too violent (event. evasive) noxae

# Factors affecting immunity

Alteration of the immune system due to:

- Aging
- Sex and hormonal influences
- Malnutrition
- Toxins (environmental, chemicals, ...)
- Trauma, burns, surgery
- Medication incl. immunosuppressive drugy, anaesthesia
- Concurrent diseases (diabetes mellitus, chronic renal failure, malignancy, HIV, ...)
- Stress, sleep disturbance, psychological well-being, ...

# Exercise immunology

- Dose and type of exercise dependent effect on immunity
- Moderate exercise enhances immune functions, reduces stress
- Rise in number of blood phagocytes and their activity during the exercise and approx. 2-4 hours after it (if > 30 min), up to 24 hours after prolonged exercise
- Increased cytotoxicity of NK cells
- Increase in lymphocytes in blood
- Regular exercise may protect against dangerous systemic low-grade inflammation (due to production of antiinflammatory cytokines)

# Exercise immunology

- Intense and/or long-duration exercise → immune impairment, incl. suppression of lymphocytes, possible increased risk of infection
- Suppression of the NK cell activity, even several hours after the exercise (vigorous training – repeated decline – possible cumulative effect?)
- High intensity exercise (>80% of maximal oxygen consumption) → immune function suppression + tissue damage → acute-phase response with complement activation, release of cytokines
- Immune system recovery in 6-24 hours

# Clinical implications

- Regular exercise in aging people may prolongate normal function of the immune system (lower decline, better immunologic balance, delay of age- and/or disease associated apoptosis (brain, heart )
- Lower inhibition of immune system after intense exercise in aged patients (x young) – such exercise possible

# Clinical implications

- During mild viral/bacterial infection exercise in otherwise healthy people possible, if symptoms located above the neck („neck check“) – sneezing, throatache, rhinitis – and are not worse after 10 minutes of moderate activity.
- If headache, head throbbing start after short term activity → stop and rest
- If systemic signs (fever, fatigue) or symptoms below the neck (cough, diarrhea, vomiting, muscle/joint ache → no exercise

# Immunity

**Innate:** not adaptive, non-specific

no immunologic memory (not stronger with more exposures)

**Adaptive (specific):**

- specific recognition and response to the particular antigen
- effective reaction to diverse pathogenes/antigenes
- memory – rapid response to subsequent exposure to the specific antigen
- activation of other defense mechanisms



# Phases of immune response

- Recognition: receptors (innate non-specific, later adaptive specific) binding to the pathogene
- Amplification: start of reaction, production and/or release of humoral factors incl. cytokines (soluble mediators), activation and/or proliferation of immune cells
- Effector phase: removal of antigenes (phagocytosis, lysis, neutralization, ...)
- Termination of the immune response (very important, if not complete – tissue damage and/or chronic inflammation possible)
- Memory – specialized long-living T- and B-lymphocytes

# Non-specific defenses of innate immunity

- Mechanic barrier functions: skin + mucosa (epithelium, cilia in respiratory tract)
- Secretory factors: lysozyme in secretions (tears), acid pH in stomach, vagina, acid urine
- Microbiome colonisation: commensal microorganisms preventing overgrowth of pathogenes

# Innate immunity

- **Cells:** neutrophils, macrophages (phagocytosis, killing of bacteria), eosinophils (antiparasitic, allergic response), basophils, natural killer cells, mast cells
- **Complement:** complex system of interacting plasma proteins, effector mechanism for specific immunity, or direct activation possible
- **Toll-like receptors** on macrophages, neutrophils, dendritic cells; if activated by binding of pathogenes, induce the secretion of pro-inflammatory cytokines
- **Rapid response** - early host response

# Mechanisms of nonspecific immunity

- Fever
- Inflammation
  - extravasation
  - phagocytosis
  - complement
- NK cells
- Interferons - against viral infection

# Natural killer cells

- **NK cells:** subtype of large granular cytotoxic lymphocyte that constitute a major component of the innate immune system. NK cells are able of direct killing of cells infected by viruses, intracellular pathogens, play a major role in the anti-tumor immunity

# Adaptive immunity

- **Pre-activation** necessary (days – weeks)
- Threat present for longer time at a higher level (activation threshold)
- **Active** immunity: **natural** contact with the antigen or **artificial** (vaccination) – usually permanent/long standing activity
- **Passive** immunity: **natural** transmission of antibodies (placenta, breast milk) or **artificial** (injection of preformed antibody/antitoxin) – temporary activity

# Cell-mediated adaptive immunity

- Direct cellular reaction to antigens
- Mediated by T-lymphocytes:
  - cytotoxic T-cells CD8+, direct killing
  - helper T-cells CD4+, cytokine production – activation of other immune mechanisms incl. innate immunity, inflammation
  - regulatory/suppressor T-cells – prevention of responses against self-antigens and commensal microorganisms

# Cytokines

- Mediators produced by many cells, incl. lymphocytes and macrophages
- Regulation of lymphocyte proliferation / maturation
- Attraction of immune cells into the focus of inflammation
- Activation of variable immune cells functions
- Stimulation of hemopoiesis



# Humoral immunity

- Mediated by antibodies (serum globulins), which are produced by plasma cells, i.e. differentiated B-lymphocytes
- Plasma cells mature when exposed to antigen
- Memory cells can react more quickly to later exposures to the same antigen
- Immunoglobulins directly attack antigens, activate the complement system, stimulate some hypersensitive reactions

# Major Histocompatibility Complex

- A highly variable genetic locus on chromosome 6, which codes for cell surface compatibility
- Also called HLA (Human Leukocyte Antigens)
- Membrane proteins presenting antigens for recognition by T-cells, which subsequently produce cytokines for regulation of both cellular and humoral immunity.
- Recognition and tolerance of all self-cell, all un-recognized cells will NOT be tolerated
- Certain MHC subtypes (alleles) associated with increased incidence of some autoimmune diseases

# Immunological tolerance

Immune system distinction between self and non-self

“Thymic education”

T cells that might react with self-antigen  
are eliminated in the thymus  
(clonal deletion; early mechanism)

Clonal anergy – possible autoreactive cells are formed but are not  
activated against certain antigens  
(later mechanism)

# Cancer immunology

## Immune surveillance

NK cells - early defense mechanism

MHC Class I activates these cells;

many tumor cells lack MHC Class I

## Cytotoxic T cells - antigen specific

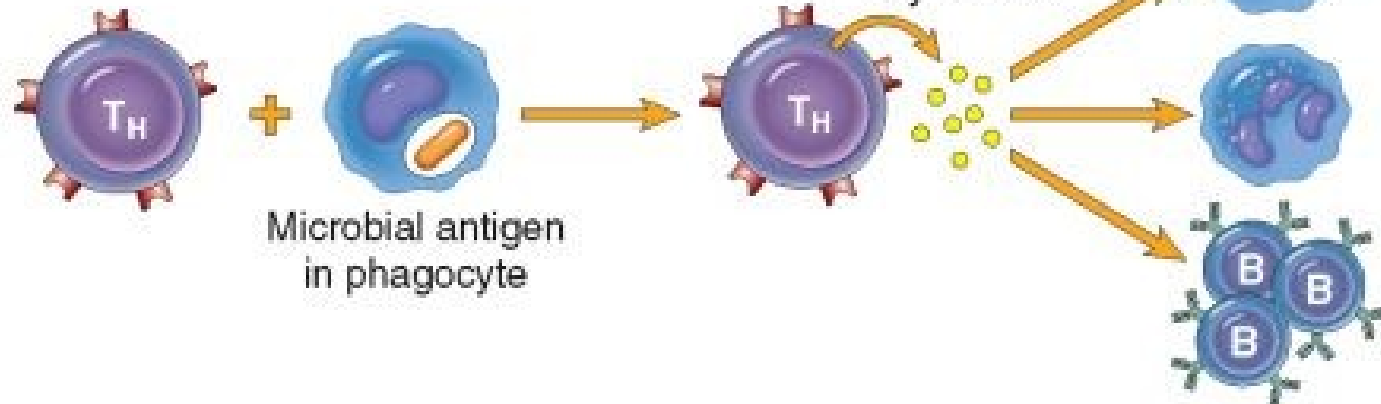
(both types of cells have similar killing mechanisms)

### B lymphocyte



Antibody secretion

### CD4+ helper T lymphocyte

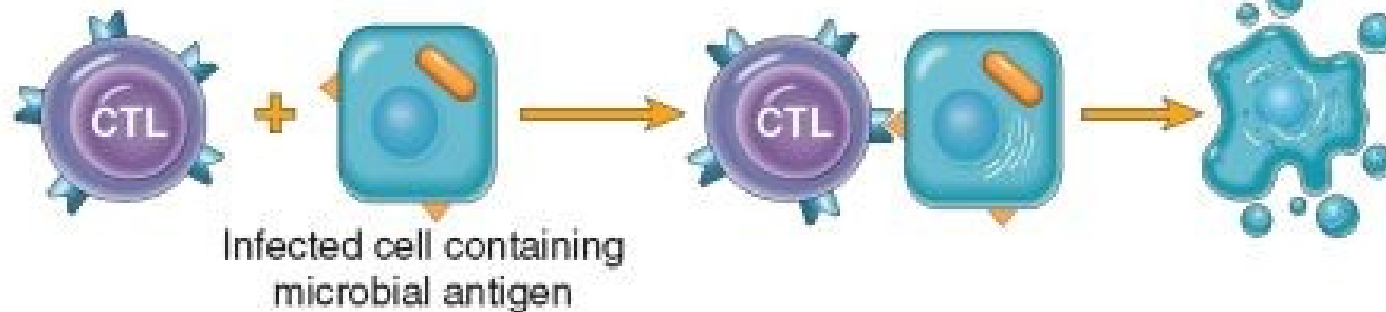


Activation of macrophages

Inflammation

Stimulation of B lymphocytes

### CD8+ cytotoxic T lymphocyte



Killing of infected cell

# Disorders of the immune system

## **Exaggerated immune reaction**

- Hypersensitivity reactions
- Autoimmune disorders

## **Transplantation immunology/immunopathology**

## **Defective immune reaction**

- Immunodeficiency (primary, secondary)

# Hypersensitivity reactions

- sensitisation (previous exposition to an antigen) + repeated exposure → possible pathologic (excessive) response: hypersensitivity – imbalance between effector mechanisms of immune responses and control (+limiting) mechanisms
- antigens exogenous (chemicals, organic substances incl. microbes, ...); endogenous (autoimmune diseases)
- association with inheritance of particular susceptibility genes (HLA, non-HLA)

# Hypersensitivity

Classification according to the immunologic mechanism  
(→ mode of tissue injury and disease, manifestations)  
+ time of response

Commonly multiple mechanisms in any one disease

- Antibody-mediated allergies are immediate and subacute hypersensitivities
- The most important cell-mediated allergic condition is delayed hypersensitivity



# Hypersensitivity reactions contribute to:

Type I- rhinitis; asthma; hives; anaphylaxis

Type II- often directed against blood cells; various types of hemolytic anemia  
drug molecules can interact with blood cells and form immunogenic structures

Type III- immune complex disease  
usually complexes are cleared, but if not, are deposited in tissue and cause inflammation

Type IV- contact dermatitis (basis for TB skin test)

# Hypersensitivity reactions

## Immediate (type I) hypersensitivity

- Rapid immunologic reaction occurring within minutes after the combination of an antigen with antibody bound to mast cells in individuals previously sensitized to the antigen („allergen“).
- Systemic disorder or local reaction.
- Anaphylaxis; allergies; bronchial asthma (atopic forms)
- Vascular dilatation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation

# Immediate (type I) hypersensitivity

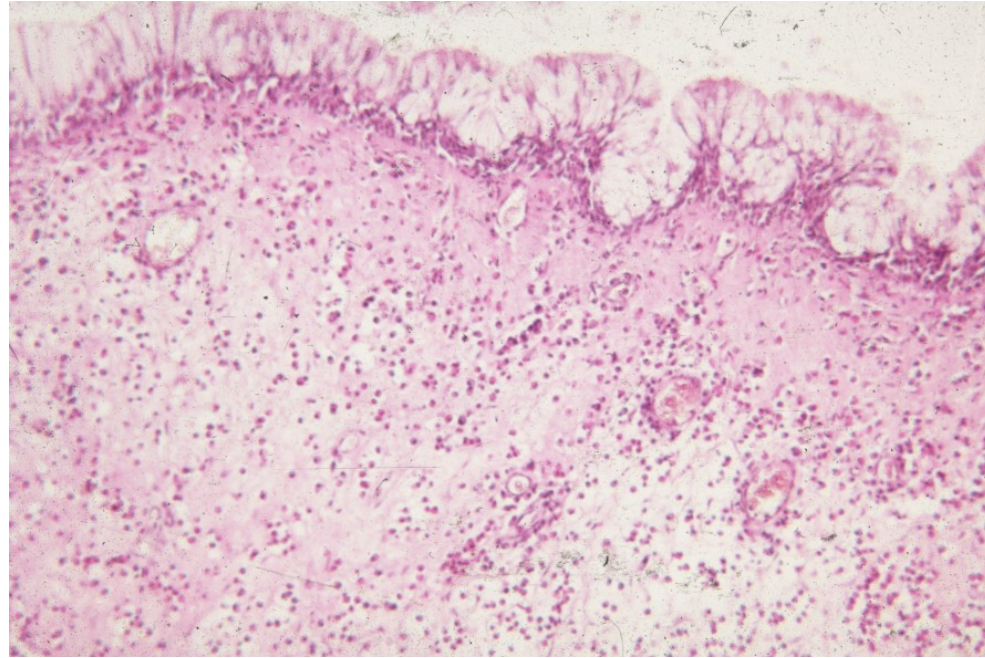
**Anaphylaxis:** systemic reaction mostly after injection of an antigen into a sensitized individual. In minutes → shock (may be fatal).

- Causes: foreign proteins, polysaccharides, drugs (penicillin), food (nuts, shellfish), insect toxins
- Starts with itching, hives, and skin erythema
- Contraction of bronchioles → respiratory distress. Laryngeal edema → hoarseness
- Vomiting, abdominal cramps, diarrhea
- Vascular shock, widespread edema

# Immediate (type I) hypersensitivity

- Local reactions: diverse, according to the entry of the allergen. Localized cutaneous swellings (skin allergy, hives);  
nasal and conjunctival discharge (allergic rhinitis and conjunctivitis);  
hay fever; bronchial asthma;  
allergic gastroenteritis (food allergy).

# Allergic rhinitis



# Atopy

- **Genetically determined susceptibility to immediate hypersensitivity reactions.**
- **Atopy:** predisposition to develop localized immediate hypersensitivity reactions to a variety of inhaled and ingested allergens.
- ↑ serum IgE levels,
- Positive family history of allergy in 50% of atopic individuals.
- Atopic eczema, allergic rhinitis, asthma (+ secondary hyper-responsiveness of bronchial mucosa to non-specific irritants, e.g. cold, tobacco smoke,... Secondary neural triggering.)

# T cell-mediated (type IV) hypersensitivity

- Contact dermatitis; multiple sclerosis; type I diabetes; rheumatoid arthritis; inflammatory bowel disease (i.e. Crohn disease); tuberculosis
- Perivascular cellular infiltrates; edema; granuloma formation; cell destruction
- Fever, arthralgia, enlarged lymph nodes, hives (urticaria)

# T cell-mediated (type IV) hypersensitivity

- **Rheumatoid arthritis:** unknown antigen in joint synovium; role of antibodies? Chronic arthritis with inflammation, destruction of articular cartilage and bone
- **Crohn disease:** unknown antigen; role for commensal bacteria; chronic intestinal inflammation, obstruction, risk of fistulae, peritonitis

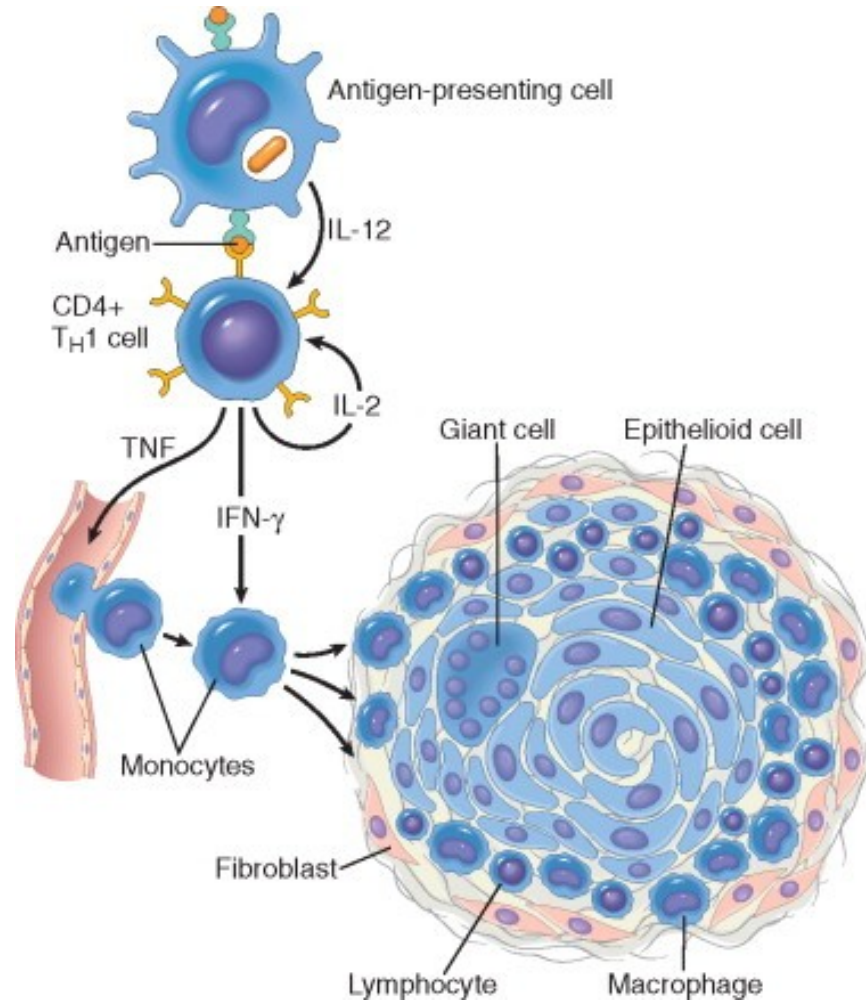


# Clinical implications

- Anaphylaxis or other type I hypersensitivity: emergency, immediate action necessary
- Type IV reactions: possible in response to lotions, gels, etc. – observation of skin reaction
- In people with known hypersensitivity – skin test
- Latex sensitivity/allergy in a therapist possible

# Granulomatous inflammation

- Persistent or nondegradable antigens, (tubercle bacilli)
- Infiltrate dominated by macrophages in 2-3 weeks.
- Activated macrophages transform into epithelium-like cells **epithelioid cells**.
- **Granuloma**: microscopic aggregation of epithelioid cells usually surrounded by a layer of lymphocytes.
- **Granulomatous inflammation** typically associated with strong T-cell activation with cytokine production



from Robbin's Pathologic Basis of Disease

# AUTOIMMUNITY

- Ability of immune system to differentiate between self and non-self antigens
- Immune system response against self antigens

# Autoimmune diseases

- *Autoimmunity arises from a combination of the inheritance of susceptibility genes, which may contribute to the breakdown of self-tolerance, and environmental triggers, such as infections and tissue damage, which promote the activation of self-reactive lymphocytes.*
- Autoantibodies (AA) in clinically normal people.
- Physiologic AA in removal of breakdown products after tissue damage (antigen-antibody complex removed by macrophages)
- Imbalance between control mechanisms (normally preventing pathologic self-reactivity) and pathways leading to the generation and activation of pathogenic effector lymphocytes.

# Autoimmune diseases

- Pathologic autoimmunity: presence of immune reaction specific for self-antigen
- + primary pathogenic, not secondary to tissue damage
- + absence of other cause
- Commonly uncertain „pure“ autoimmunity – term immune-mediated inflammatory diseases

# Factors influencing autoimmune disease

## Internal triggering factors

- genotype / HLA
- cytokines
- apoptosis genes
- primary immunodeficiency
- hormones

## External triggering factors

- infections
- UV
- drugs
- chemicals (including food)
- stress

# Autoimmune diseases

- *Most autoimmune diseases are **complex multigenic disorders***
- Many autoimmune diseases associated with infections, clinical flare-ups often preceded by infectious prodromes
- Disease occurrence in clusters, discordance in identical twins
- Many infectious diseases similar to autoimmune disease in pathology (Lyme disease)

# Autoimmune diseases

- Different autoimmune diseases show substantial clinical, pathologic, and serologic overlaps.
- Precise phenotypic classification often problematic.



# Autoimmune diseases

- **DISEASES MEDIATED BY ANTIBODIES AND IMMUNE COMPLEXES**

## Organ-specific autoimmune diseases

Autoimmune hemolytic anemia  
Autoimmune thrombocytopenia  
Myasthenia gravis (muscle weakness)  
Graves disease (thyroid hyperfunction)

## Systemic autoimmune diseases

Systemic lupus erythematosus (SLE)

## Diseases caused by autoimmunity or by reactions to microbial antigens

Polyarteritis nodosa (vessel wall inflammation + necrosis)

# Autoimmune diseases

## **DISEASES MEDIATED BY T-CELLS**

### **Organ-specific autoimmune diseases**

Type 1 diabetes mellitus  
Multiple sclerosis (brain)

### **Systemic autoimmune diseases** (+ possible role of antibodies)

Rheumatoid arthritis (mainly joints, soft tissues inflammation)  
Systemic sclerosis (mainly soft tissues inflammation)  
Sjogren syndrome (chronic inflammation of salivary, lacrimal glands)

### **Diseases caused by autoimmunity or by reactions to microbial antigens**

Inflammatory bowel disease (Crohn disease, ulcerative colitis)  
Inflammatory myopathies (muscles)

# Incidence of autoimmune diseases

- RA 1-3%
- Sjögren's sy 1/20 000
- Vasculitis 1/100 000
  
- Prevalence of autoimmune diseases

**5-7% of population**

# SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Chronic systemic autoimmune disease
- Cause unknown
- Affects almost any organ(s)
- Characterized by chronic inflammation

# SLE

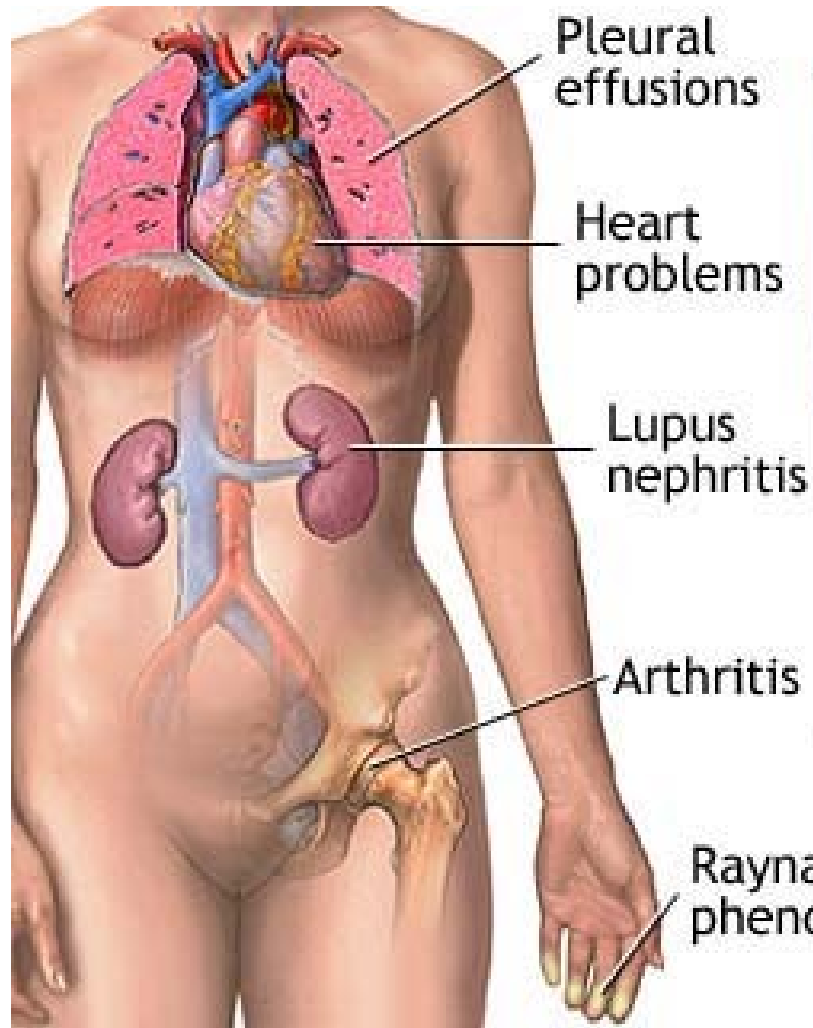
- The course of the disease is variable and unpredictable.
- Rare acute cases result in death within weeks to months.
- Appropriate therapy: flare-ups and remissions, years or even decades.
- *The most common causes of death are renal failure and intercurrent infections.*

# SLE – typical case

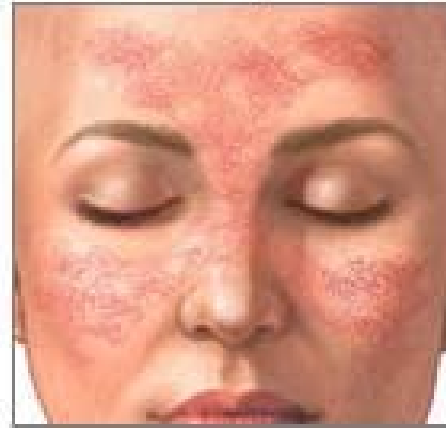
young woman with some of the following features:

- a butterfly rash over the face,
- fever,
- pain but no deformity in one or more peripheral joints (feet, ankles, knees, hips, fingers, wrists, elbows, shoulders),
- pleuritic chest pain
- photosensitivity

# SLE



Butterfly rash



Symptoms of systemic lupus erythematosus may vary widely with the individual

# Clinical features of SLE





# Special implications of SLE

- Physical and occupational therapy important part of treatment
- Individual plan, according to the phase (acute flare with mostly rest, gradual start of activities with energy conservation – fatigue common)
- Exercise to increase muscle strength, prevent osteoporosis x avoid increased stress of inflamed joints
- Limit exposure to direct sunlight
- Immunosuppression due to therapy → risk of infection

# Rheumatoid arthritis

- Systemic autoimmune disease (joints, skin, blood vessels, heart, lungs, muscles, nerves)
- Genetic factors
- Etiology unknown, combination of gen. predisposition, environment (trigger), autoimmunity
- Rheumatoid factor (RF) in 80%
- Start commonly between ages 25-50 years
- Women 3:1 men
- Prolonged morning joint stiffness ( $\geq 1$  hour)

# Rheumatoid arthritis

- Chronic nonpurulent proliferative inflammation of synovial joints, symmetrical
- Proliferation of synovial lining cells, oedema, fibrin deposition → pannus (synovial cells + granulation tissue + inflammatory cells) →
- Erosion of articular cartilage and adjacent bone (osteoclasts) →
- Fibrous ankylosis → bony ankylosis

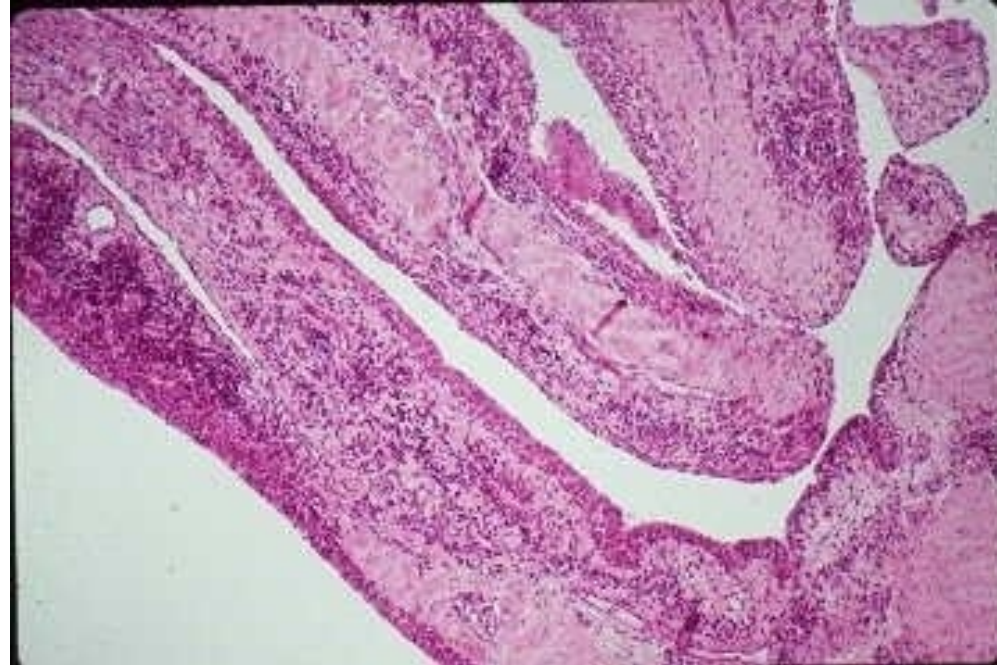
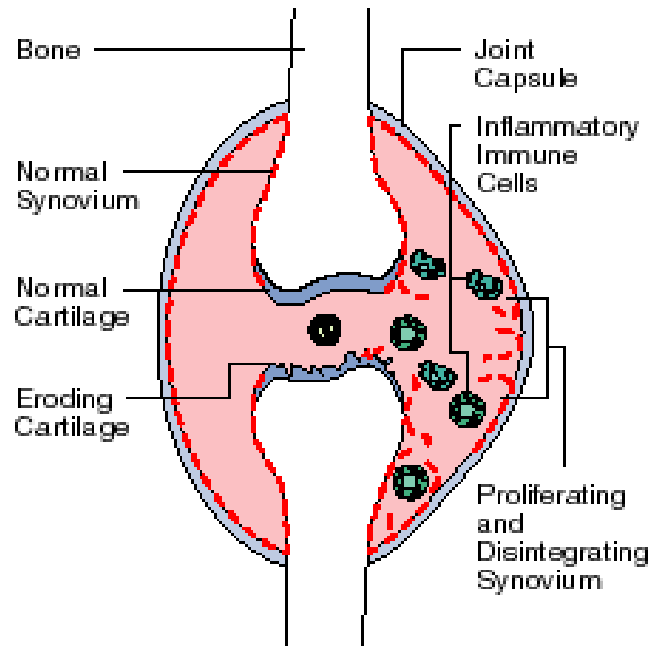
Variable course, usual start in hands or other small joints.

Arthritis + morning stiffness

Worsening limitation of motion

Rheumatoid nodules in organs or tissues – skin, lungs (!x ca), myocardium,...

Systemic signs (fatigue, malaise, weight loss, fever, ... )





# Special implications

- Part of diagnostic staff (localisation, type and duration of joint pain)
- Signs of possible progression (increased intensity of pain, more joints affected)
- True arthritis – pain during active + passive motion x tendinitis – more in active motion
- Patient education (type of exercise)
- Functional status and rehabilitation

# Systemic sclerosis

- Chronic inflammation with progressive interstitial and perivascular fibrosis in the skin, subcutaneous tissue, muscles and multiple organs
- gastrointestinal tract, kidneys, heart, muscles, and lungs (interstitial fibrosis) frequently involved
- death from renal failure, cardiac failure, pulmonary insufficiency, or intestinal malabsorption
- *limited scleroderma*, in which the skin involvement is often confined to fingers, forearms, and face.

# Systemic sclerosis

- female-to-male ratio of 3 : 1, with a peak incidence in the 50- to 60-year age group
- Raynaud's phenomenon: episodic vasoconstriction of the arteries and arterioles of the extremities, in virtually all patients and precedes other symptoms in 70% of cases.
- Dysphagia attributable to esophageal fibrosis and its resultant hypomotility in more than 50% of patients



# Organ-specific autoimmune diseases

## Neuromuscular system

- Myasthenia gravis
- Autoimmune polyneuritis
- Multiple sclerosis

# Diabetes

Hyperglycaemia

Different mechanisms cause different forms

Genetic and environmental component to all forms

Diabetes gives rise to complications;

microvascular- nephropathy, neuropathy, retinopathy

macrovascular - cardiovascular disease

Two major forms of diabetes:

Type 1 diabetes (autoimmune)

Type 2 diabetes (metabolic)

# Multiple sclerosis

- autoimmune brain disorder, genetic + environmental factors (infection as trigger), T lymphocytes reaction against myelin + macrophagic activation by cytokines – demyelination
- Brain white matter plaque (active, inactive), gliosis – sclerosis
- muscular weakness, paraesthesia, sensoric dysfunction (ocular), etc.

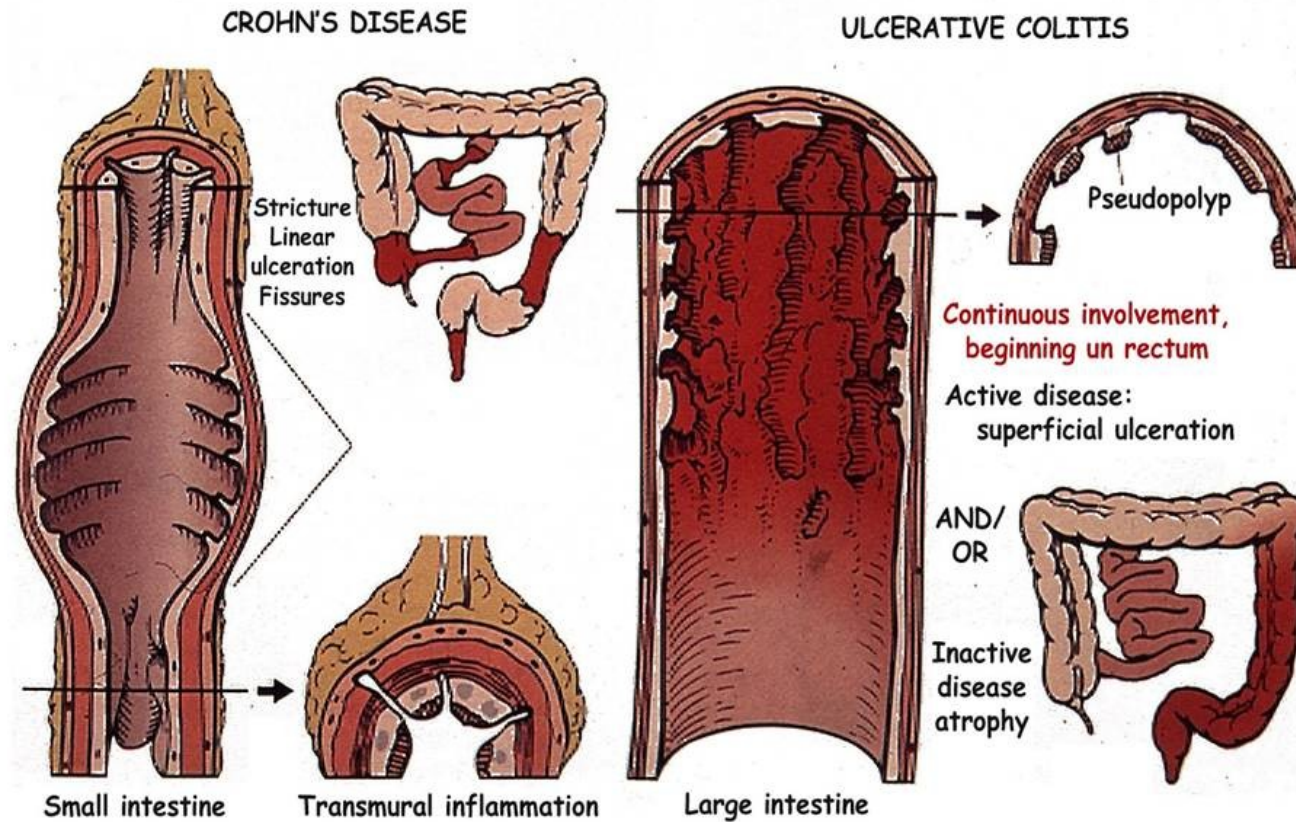
# Myasthenia gravis

Disease marked by progressive weakness and loss of muscle control

Classified as a B cell disease

Autoantibodies against nicotinic acetylcholine muscle receptors

# IBD – inflammatory bowel diseases



# IMMUNODEFICIENCIES

- **Primary** – genetic, uncommon
- **Secondary** – acquired, very common

# Primary immunodeficiencies

- Depends on the stage of immune development that is affected
- The earlier the defect, the more severe the effect
- SCID (severe combined immunodeficiency syndrome)  
essentially no protection against infection  
difficult treatment (bone marrow transplants, etc.)

# Common variable immunodeficiency CVID

- relatively common, heterogeneous group of disorders (dg. by exclusion), both sexes, children - adolescents
- hypogammaglobulinemia
- sporadic and inherited forms
- B cells in normal numbers, not able to differentiate into plasma cells
- abnormalities in T helper cell-mediated activation of B cells
- hyperplastic B-cell zones in lymphoid tissue



## SECONDARY IMMUNODEFICIENCY

Due to impaired synthesis and function:

- protein, vitamin and energy deficiency in malnutrition, cachexia in disseminated cancer, anorexia, alcoholism
- prevalent monoclonal Ig in some lymphoproliferative diseases
- bone marrow infiltration or fibrosis (leukemia, myelofibrosis)
- suppression of cell mediated immunity due to acute viral infection (CMV, EBV, measles, etc.), bacterial and protozoal infection – macrophagic dysfunction (leprosy, leishmaniasis)

# SECONDARY IMMUNODEFICIENCY

- iatrogenic (immunosuppressive and cytostatic drugs, radiotherapy, splenectomy – pneumococcus sepsis)
- diabetes mellitus and other metabolic diseases
- chronic stress
- sarcoidosis (↓ Tcell function)
- certain age groups (old, newborn, immature infants)

**Increased catabolism or loss:** nephrotic syndrome and renal failure, inflammatory intestinal diseases (IBD, lymphangiectasia)

# SECONDARY IMMUNODEFICIENCY

## Humoral immunodeficiency

- intestinal lymphangiectasia, IBD → ↓ all Ig classes, commonly + lymphopenia
- nephrotic sy, chronic diarrhea → ↓ IgG
- iatrogenic immunosuppression/cytostatic therapy
- B-cell malignancies
- Splenectomy – spleen B-cell – Ab x polysaccharide antigens – encapsulated microorganisms (pneumococci)

# SECONDARY IMMUNODEFICIENCY

## Cellular immunodeficiency

- temporal after acute viral infection (CMV, EBV, measles, etc.)
- AIDS

# SECONDARY IMMUNODEFICIENCY

## Combined immunodeficiency

- Severe general metabolic problems (DM, renal insufficiency), malnutrition, anorexia, chronic alcoholics – inadequate hormones, glucose, vitamins level

# Clinical implications

- Increased risk of infections + commonly poor physiologic and psychologic health status + comorbidities + invasive procedures
- **Infection control strategy necessary**
- Minimize infection reservoirs (you, the client, reusable equipment, invasive devices)
- Stop the transmission (hand washing, clean/sterile techniques and equipment, face mask, maintain skin integrity)

# HIV / AIDS

- Pandemic infection, affecting cells of the immune system → possible problems in any organ system
- Infection by opportunistic microorganisms → inflammation, tumors
- Direct influence of HIV on nervous system
- Common co-infection with other infection (hepatitis C, hepatitis B, tuberculosis), esp. in high-risk behaviour

# AIDS epidemics

- HIV infection in Europe: National epidemics concentrated among key populations at higher risk (men who have sex with men – MSM, injecting drug users; prisoners, sex workers, sexual partners of key population).



# AIDS epidemics

- Europe, Australia and Canada: mortality rates among people living with HIV in the first five years after infection now ~ in the HIV-uninfected population
- Mortality among HIV-infected people increases with the duration of infection
- Increasing complications of chronic HAART – highly active antiretroviral therapy

# HIV ISSUES

- Blood safety
- HIV treatment: antiretroviral therapy
- Prevention of mother-to-child transmission
- Co-management of tuberculosis and HIV treatment
- HIV testing in the general and most-at-risk population

# HIV / AIDS - transmission

- Exchange of body fluids (blood, semen) – high-risk behaviour
- High-risk unprotected sex (vaginal, oral, anal), MSM
- Females: 2x↑ risk (HIV viral load in semen important), sexually transmitted diseases (STD) further ↑ the risk (defect in mucosa)
- Children - during pregnancy, labor, breastfeeding
- Infected equipments (needle – intravenous drug use; 0,3% after needlestick injury in healthcare workers; tattoo, ...)
- **NOT transmitted:** casual social or household contact, cups, drinking fountains, unbroken skin contact, sweat, tears, nonbloody saliva, urine, faeces...
- **Postexposure prophylaxis** possible

# Phases of HIV infection

- **Acute retroviral syndrome** (3-6 wks after infection, in 40-90%, self-limited in 2-4 wks)
- **Chronic phase** (clinical latency, persistent generalized lymphadenopathy – PGL)
- **Progression to AIDS** (AIDS-related complex – ARC, AIDS indicator conditions: constitutional, neurologic, opportunistic infection, neoplasm)

# Acute HIV infection

- **Suspect:** Signs or symptoms of acute HIV infection with recent (within 2–6 weeks) high risk of exposure
- **Possible signs:** fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation.

# Acute HIV infection

- **High-risk exposures** include sexual contact with a person infected with HIV or at risk of HIV, sharing of injection drug use paraphernalia, or contact of potentially infectious blood with mucous membranes or breaks in skin.
- **Differential diagnosis:** Epstein-Barr virus (EBV)- and non-EBV (e.g., cytomegalovirus [CMV])-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis

# Opportunistic infections and neoplasms

- **Protozoal and helminthic** cryptosporidiosis, toxoplasmosis, giardiasis, etc.)
- **Fungal** (Pneumocystis, candidiasis, cryptococcosis, coccidiomycosis, histoplasmosis)
- **Bacterial** (mycobacteriosis – atypical, TB; salmonellosis, nocardiosis)
- **Viral** (CMV, Herpes simplex, Varicella-zoster, progressive multifocal leukoencephalopathy – JC polyoma virus)
- **Neoplasms** ( Kaposi sarcoma – HHV 8, B-cell non-Hodgkin lymphomas, primary brain lymphomas – EBV, aggressive cervical and anal carcinomas – HPV)

# SKIN + ORAL INFECTIONS

- Chronic, relapsing, non-healing
- Commonly ulcers
- EBV + HIV – oral hairy leukoplakia
- Candida
- HSV, VZV



# Oral hairy leukoplakia



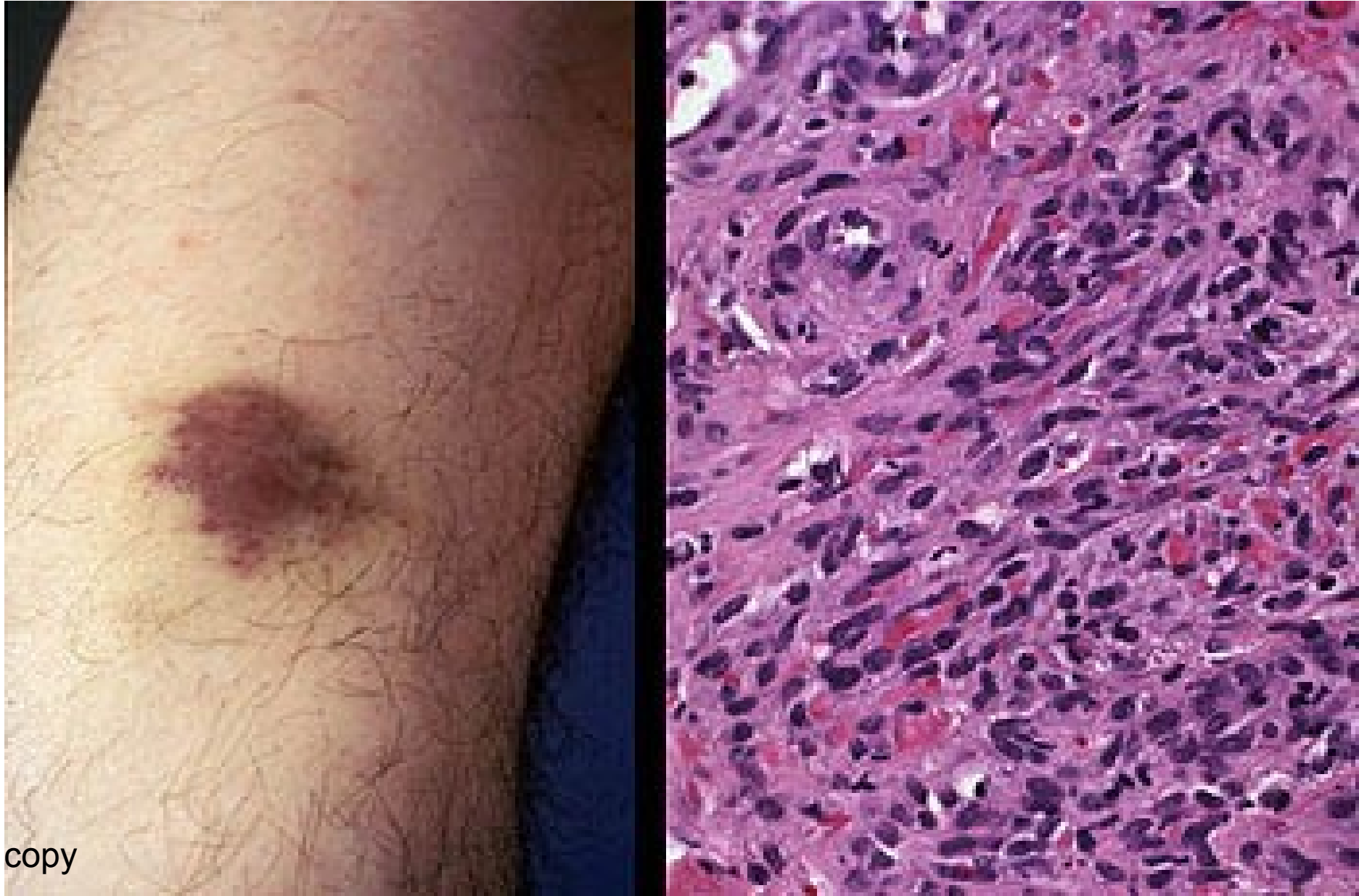
# Musculoskeletal manifestations

- Myalgia/arthralgia
- Rheumatologic manifestations incl. joint inflammation
- Musculoskeletal pain syndrome / HIV wasting syndrome
- Delayed healing

# HIV-associated neoplasia

- HHV-8: Kaposi's sarcoma
- EBV: non-Hodgkin's malignant lymphoma, primary brain ML
- HPV: aggressive anal, cervical squamous cell carcinoma
- general increased risk of malignancy

# Kaposi sarcoma



copy

# HIV lymphoma

- Solitary lump or nodule, swelling, nonhealing ulcer
- The swelling may be ulcerated or may be covered with intact, normal-appearing mucosa.
- Usually painful, rapid growth.
- Common association with EBV
- Several histopathologic types, atypical localization

# Human papilloma viruses

- Human papilloma virus lesions appear most commonly in immunocompromised individuals.
- Diagnosis based on history, clinical appearance, and biopsy.
- Common in early HIV infection.
- Spiky warts, raised, cauliflower-like appearance.

# Noninfectious HIV-related comorbidities:

- The premature aging process in HIV-infected people
- 2x ↑ risk of myocardial infarction
- ↑ risk of osteoporosis incl. fractures (even in adolescents!)
- ↑ risk of chronic renal failure
- Non-AIDS tumors

# HAART complications

- Diarrhea, nausea , and vomiting.
- Lipodystrophy: fat in adipous tissue redistributed to other regions, i.e.face and limbs → thin, breasts, stomach and/or neck enlarge.
- Glucose intolerance, diabetes. Lactic acidosis.
- Liver toxicity – acute hepatitis incl. liver failure. Pancreatitis.
- Nephrotoxicity
- Neuropathy
- Osteonecrosis, osteoporosis, osteopenia



# Special implications

- Protect yourself (client unaware of HIV+, untrue report of HIV status)
- Help the diagnosis (encourage HIV test in unclear clinical signs)
- Special support according to the problems (wasting, osteoporosis, ...)

# Pathology of Infectious Diseases

# Categories

**Saprophytes:** nonpathogenic; in dead organic matter

**Parasites:** living in or on an host on his the expense

– **Commensals:** normal inhabitants of skin and mucosa;

– **Pathogenic microorganisms:** Classic disease-causing pathogens

– **Opportunists or facultatively pathogenic** microorganisms:

in immunocompromised individuals in an “opportune” situation; frequently from the normal flora, may be from the surrounding environment or other germ carriers

**Pathogenicity:** capacity of a pathogen species to cause disease

**Virulence:** sum of the disease-causing properties of a strain

of a pathogenic species

# RESIDENT FLORA

- NO disease under normal conditions
- Includes bacteria, fungi, protozoa, viruses and arthropods (mites)
- Most areas of the body in contact with the outside environment harbor resident microbes; large intestine has the highest numbers of bacteria
- Internal organs, tissues, fluids microbe-free
- Bacterial flora benefit host by preventing overgrowth of harmful microbes

# OPPORTUNISTIC FLORA

- Potentially pathogenic organisms that do not cause disease in their normal habitat in a healthy person
- Organisms that gain access into the tissue through broken skin or mucous membranes
- Host already weakened or compromised by infection.

# Host involvement

**Endogenous infection** from the colonizing flora

**Exogenous infection** from invasion of host by microorganisms from external sources

**Nosocomial infection** acquired during hospitalization (urinary tract infections, infections of the respiratory organs, wound infection, sepsis)

# Host involvement

**Superinfection:** occurrence of a second infection in the course of a first infection

**Relapses:** series of infections by the same pathogen

**Reinfection:** series of infections by different pathogens

**Subclinical disease:** No noticeable signs or symptoms (inapparent infection)

# Host involvement

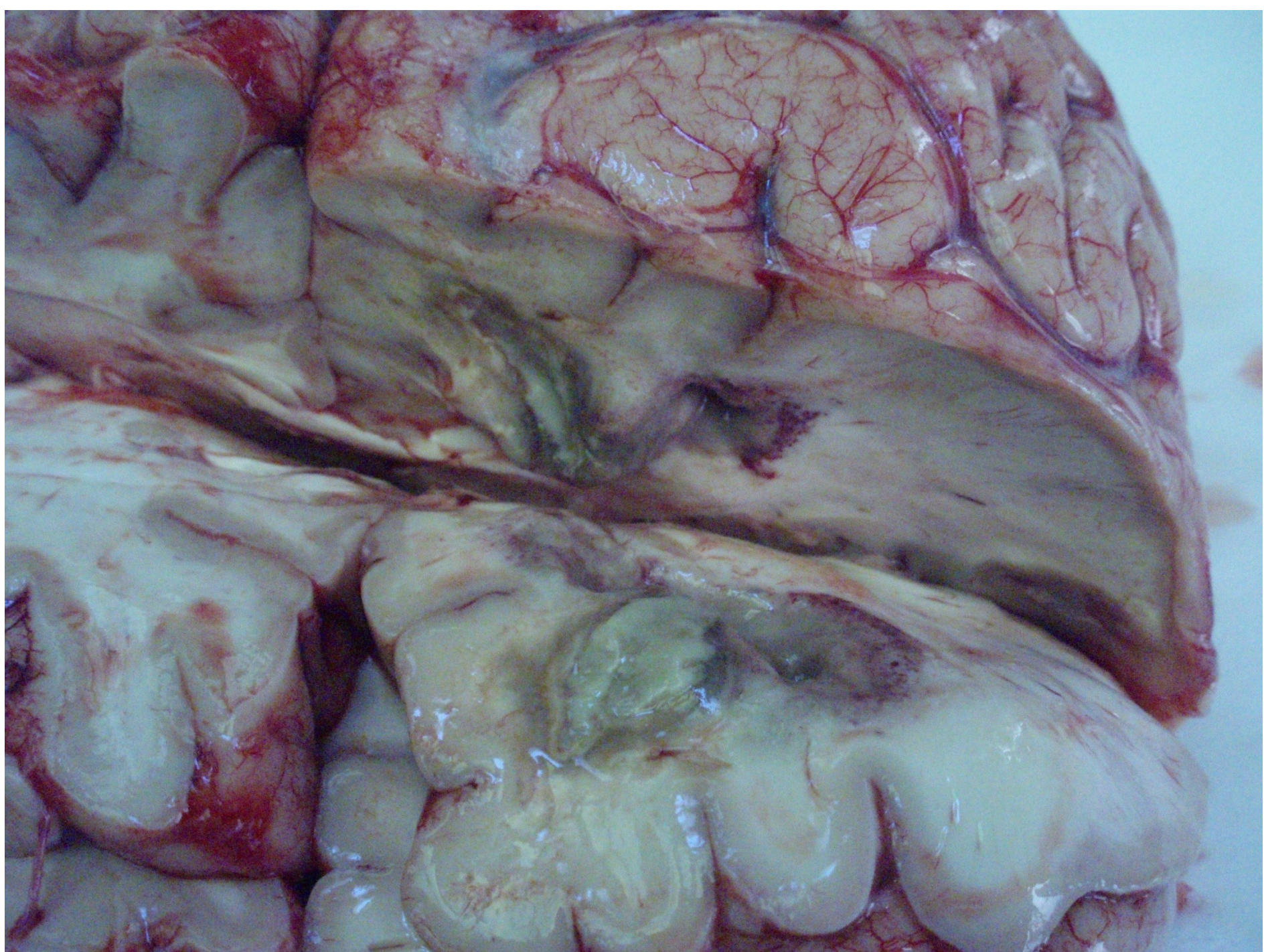
**Local infection** restricted to the portal of entry and surrounding area

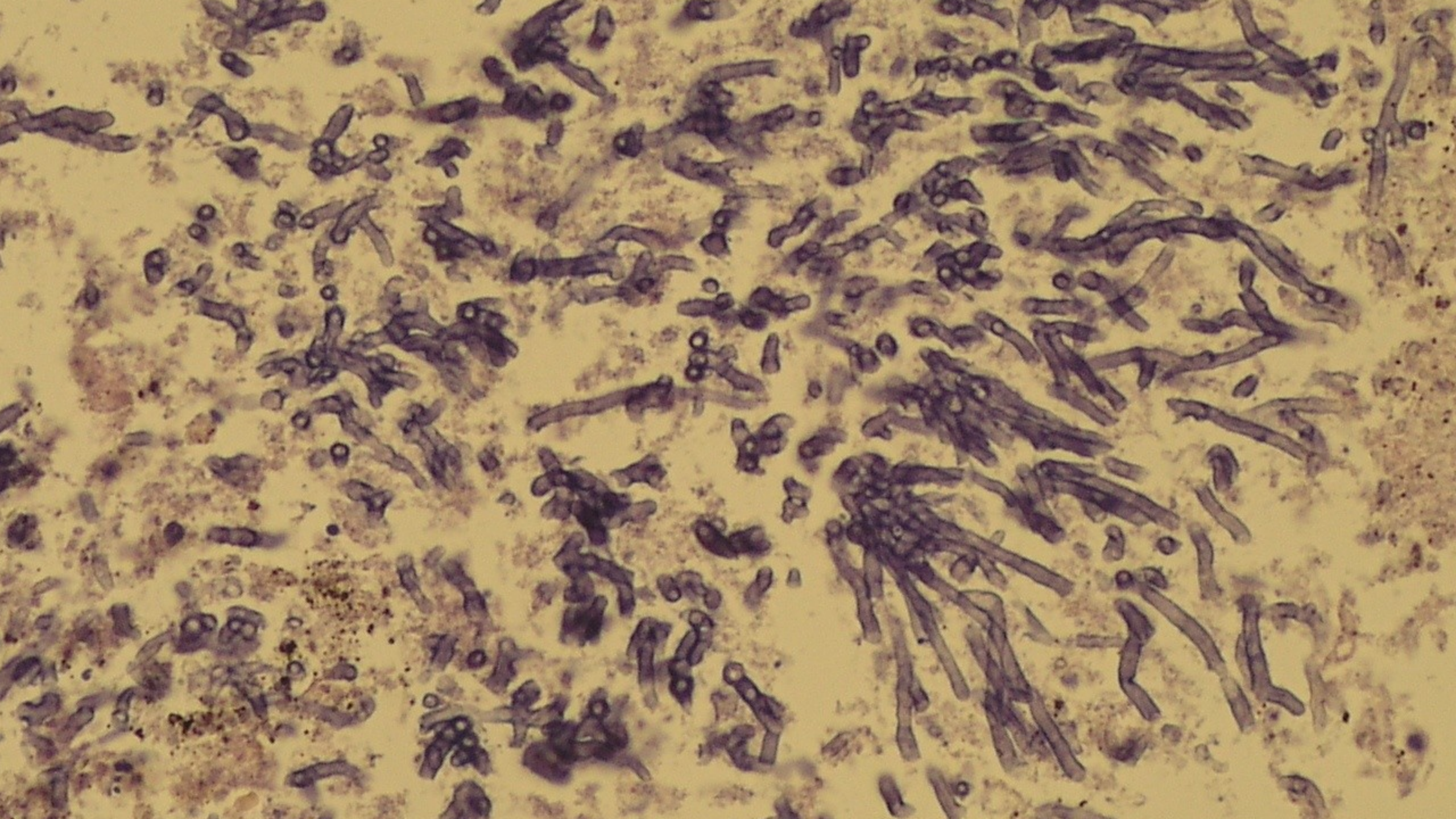
**Generalized (systemic) infection** Lymphogenous and/or haematogenous spread of pathogen from the portal of entry; organotropism; three stages: incubation, generalization, organ manifestation

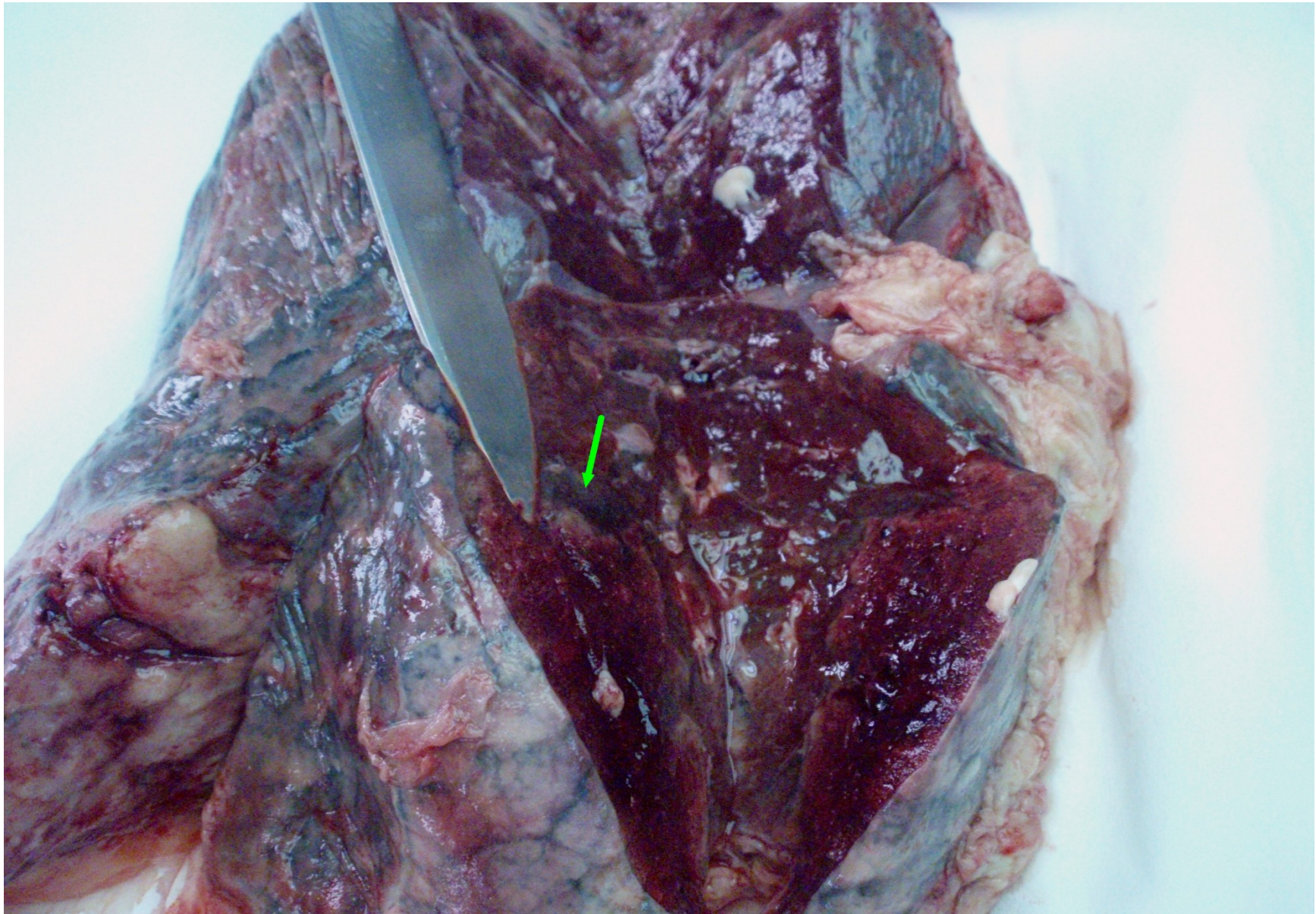


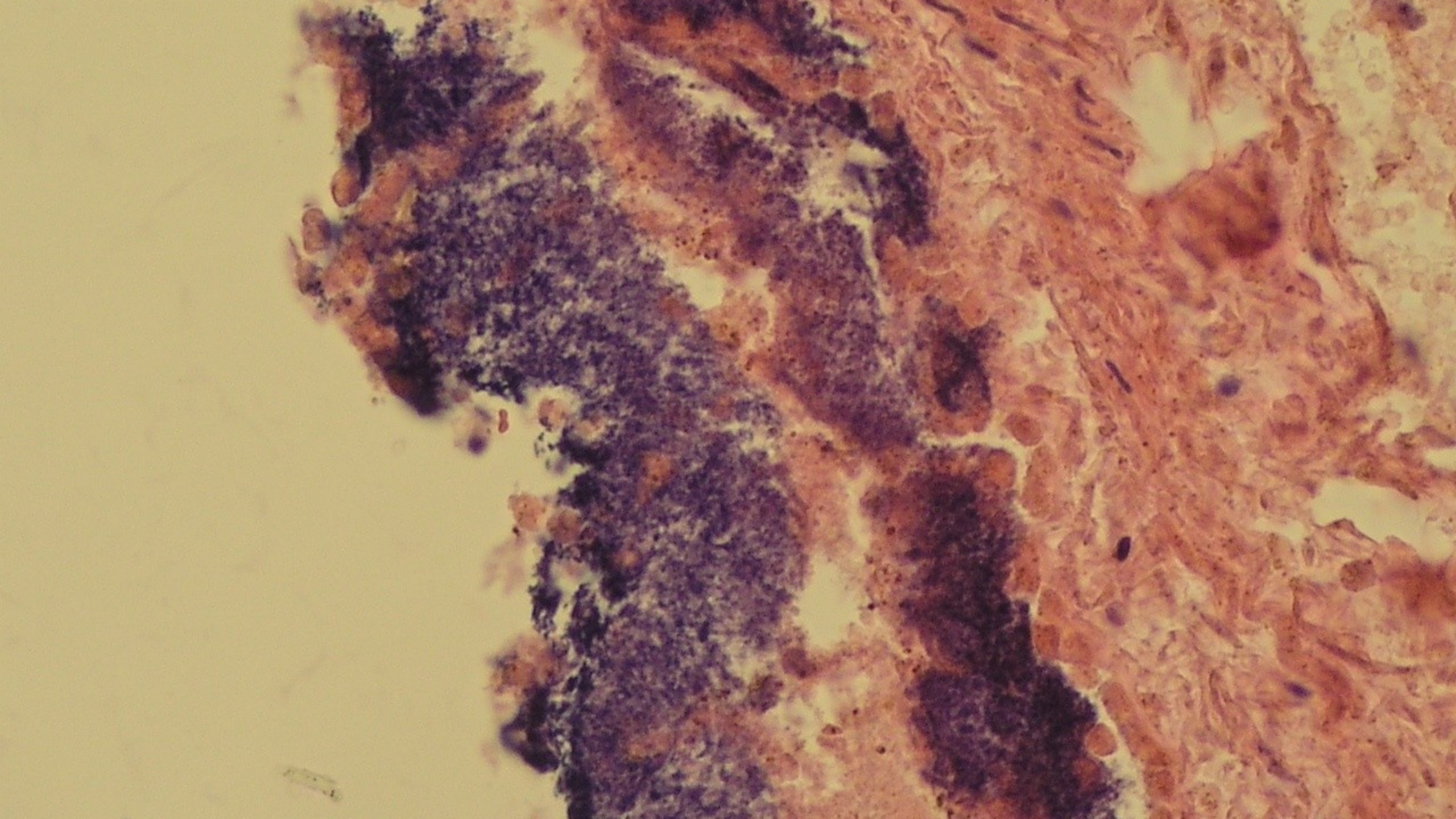
# Systemic infection

- example: immunocompromised host, mycotic infection, portal of entry – lung, skin
- generalisation - haematogenous
- organotropism – brain abscesses  
lung abscesses
- superinfection by bacteria









# Host involvement

**Sepsis** Systemic disease by microorganisms and/or their toxic products; often a localized focus of infection from which pathogens or toxic products enter the bloodstream continuously or in intermittent phases, → shock

**Septicemia** Growth of (pathogenic) bacteria in the blood

**Pyemia** Bacteria in blood in aggregates (microemboli) + toxemia, → pyemic abscess, septic infarction

**Transitory bacteremia/viremia/parasitemia** Brief presence of microorganisms in the bloodstream

# Epidemic process and epidemic factors of infectious disease

- **Source of infection (basic conditions)**

Patients (acute, chronic), covert infection, carrier, infected animal

- **Route of transmission**

Contact transmission (direct and indirect), blood-borne, soil-borne, food + water-borne, air-borne, insects, ...

- **Susceptibility of population**

- **Factors of influencing epidemic process**

nature factors, social factors

# Reservoirs of infection

- **Continual sources of infection**

- Human: AIDS, gonorrhoea
  - **Carriers** may have inapparent (subclinical) infections or latent diseases
- Animal: Rabies, Lyme disease
  - Some **zoonoses** may be transmitted to humans (zika, SARS, ...)
- Nonliving: Botulism, tetanus
  - Soil



# CONTACT TRANSMISSION

- DIRECT CONTACT - reservoir to host
- INDIRECT CONTACT - reservoir to vehicle to host.
  - Vehicle – inanimate material, food, water, drugs, biological products, ...
- DROPLET - reservoir to air (short distance) to host  
Airborne transmission - spread of agents by droplet nuclei or dust at a distance of more than 1 meter from the reservoir to host
- VECTOR

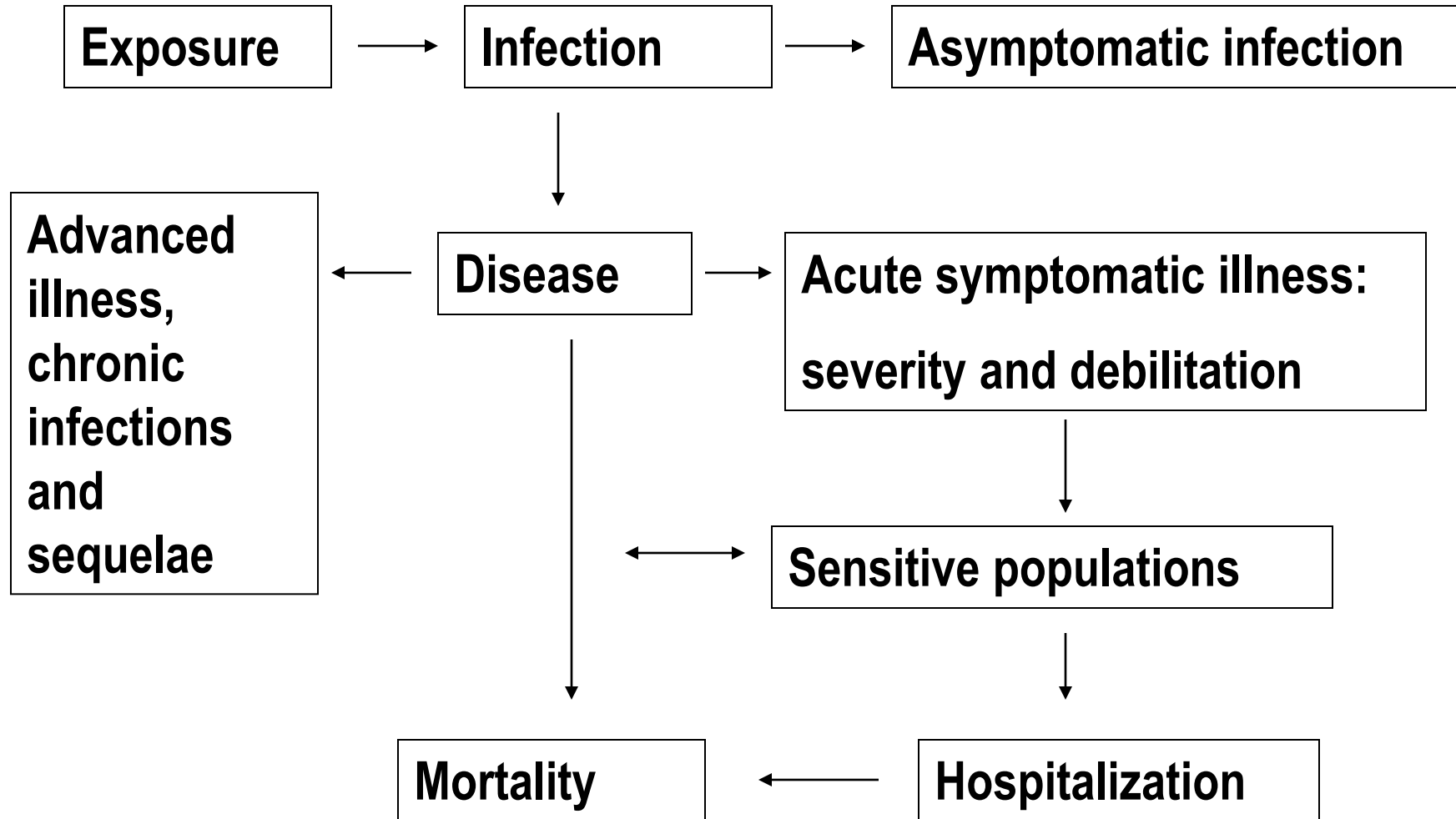
# Host factors in pathogen transmission

- Age (old age, extreme youth – prematurity, infancy)
- Immune status (inborn and/or acquired defects, incl. immunosuppressive therapy, stress, etc.)
- Concurrent illness or infirmity
- Genetic background
- Pregnancy
- Nutritional status
- Demographics of the exposed population (density, etc.)
- Social and behavioral traits

# Sensitive populations – increased infectious disease risks

- **Infants and young children**
- **Elderly**
- **Immunocompromized**
  - **Persons with AIDS**
  - **Cancer patients**
  - **Transplant patients**
- **Pregnant**
- **Malnourished**

# Outcomes of infection process



# INFECTIOUS DISEASES

- **SYMPTOMS** - subjective evidence of disease as sensed by the patient.
- **SIGNS** - objective evidence of disease as noted by an observer.
- **SYNDROMES** - a specific group of symptoms or signs which accompany a particular disease.

# Common signs and symptoms

## Signs

Fever

Septicemia

Skin eruptions

Chest sounds

## Symptoms

Chills

Fatigue, soreness

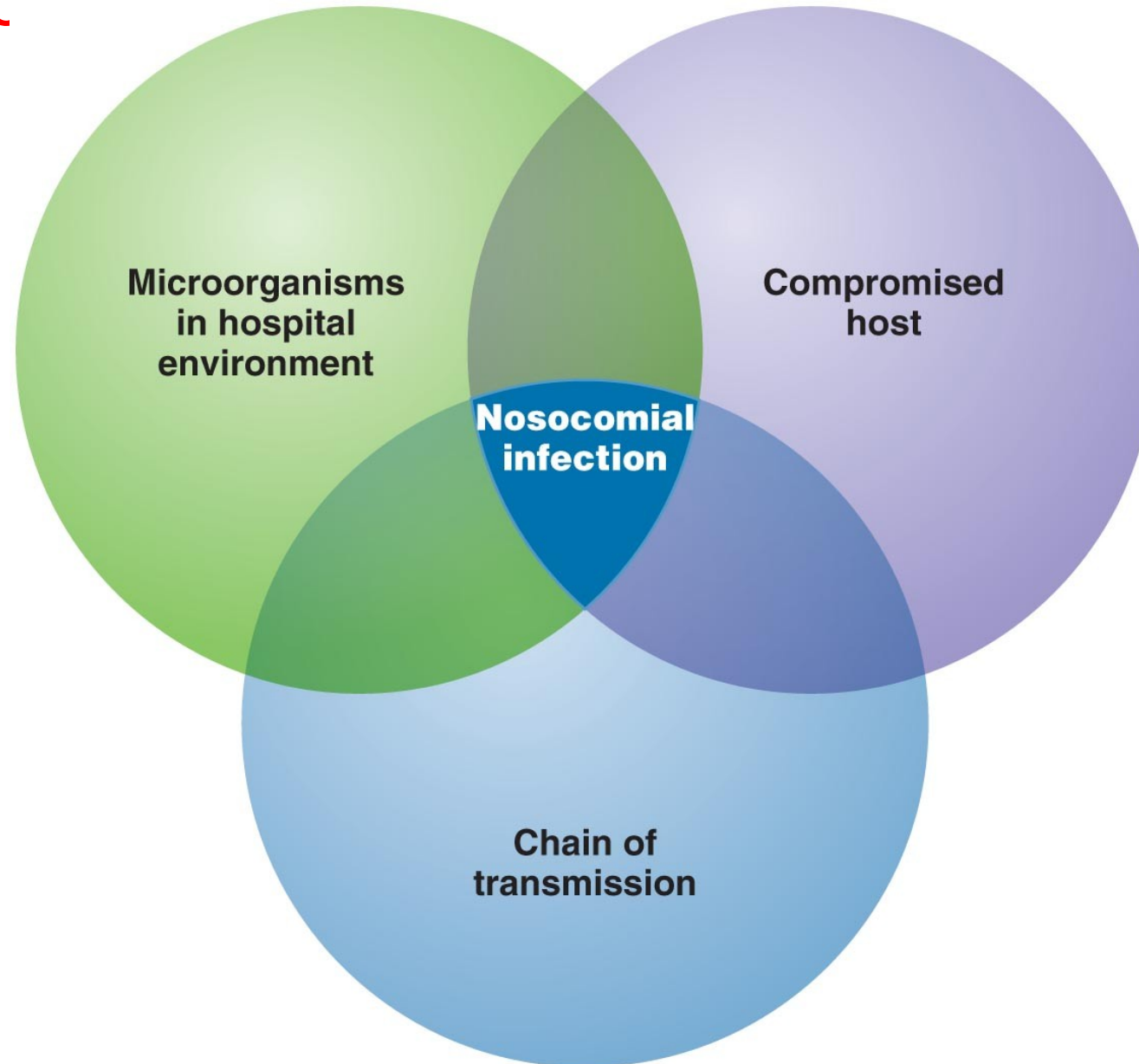
Itching

Dyspnoea

# Portals of entry

- Skin
- Gastrointestinal tract
- Respiratory
- Urogenital
- Via placenta
- Parenteral (injection, bite)

# Nosocomial infections – health care-associated infections





# Nosocomial infections

- ~ 10% of patients/clients acquire a clinically significant nosocomial infection
- 10-30% in developing countries

# Nosocomial infections

- Colonies of hospital bacterial strains develop on patient's skin, in respiratory and genitourinary tract within hours after admission
- **Risk factors:** patient related
  - iatrogenic
  - organisational

# Iatrogenic risk factors

- Medical personnel hands as source
- Invasive procedures
- Antibiotics use + prophylaxis

# Clinical implications

- Preventing of infection
- Control of transmission (airborne + droplet precaution, contact – **hand hygiene**, blood)
- Work restrictions for personnel with some infectious diseases

# Emerging infectious diseases

- Geographic spread of known infections (West Nile virus, Plasmodium falciparum - malaria)
- Local spread – environmental changes (bats – rabies; ticks – encephalitis, Lyme borreliosis; mosquitoes – dengue, zika)
- Crossing of interspecies barrier (SARS coronavirus, Ebola, BSE- bovine spongiform encephalopathy)
- Re-emerging infections, new strains event. resistant (TBC, Vibrio cholerae, influenza H5N1, H1N1)

# Respiratory tract infections

- **Viral**

Rhinoviruses, Influenza,

- **Bacterial**

Str. pneumoniae, Haemophilus infl., Chlamydia, TB,

- **Fungal**

Histoplasmosis, Coccidioimycosis, Pneumocystis

# Lower respiratory tract

- **Pneumonia – lobar** (pneumococcus, Klebsiella); **bronchopneumonia** (variable pyogenic bacteria)  
**atypical (interstitial):** viral – influenza, herpetic viruses,  
small bacteria (Mycoplasma, Legionella, Chlamydia)  
fungal – Aspergillus, Pneumocystis, Cryptococcus, Candida,  
**granulomatous:** TB, MAC, Histoplasma

# Influenza

- Acute respiratory illness caused by influenza viruses.
- Typical symptoms-fever, chills, myalgia, headache, sore throat, cough.
- Serious cases in young children and elderly.



# Influenza manifestations

- Incubation period: 1-3 days

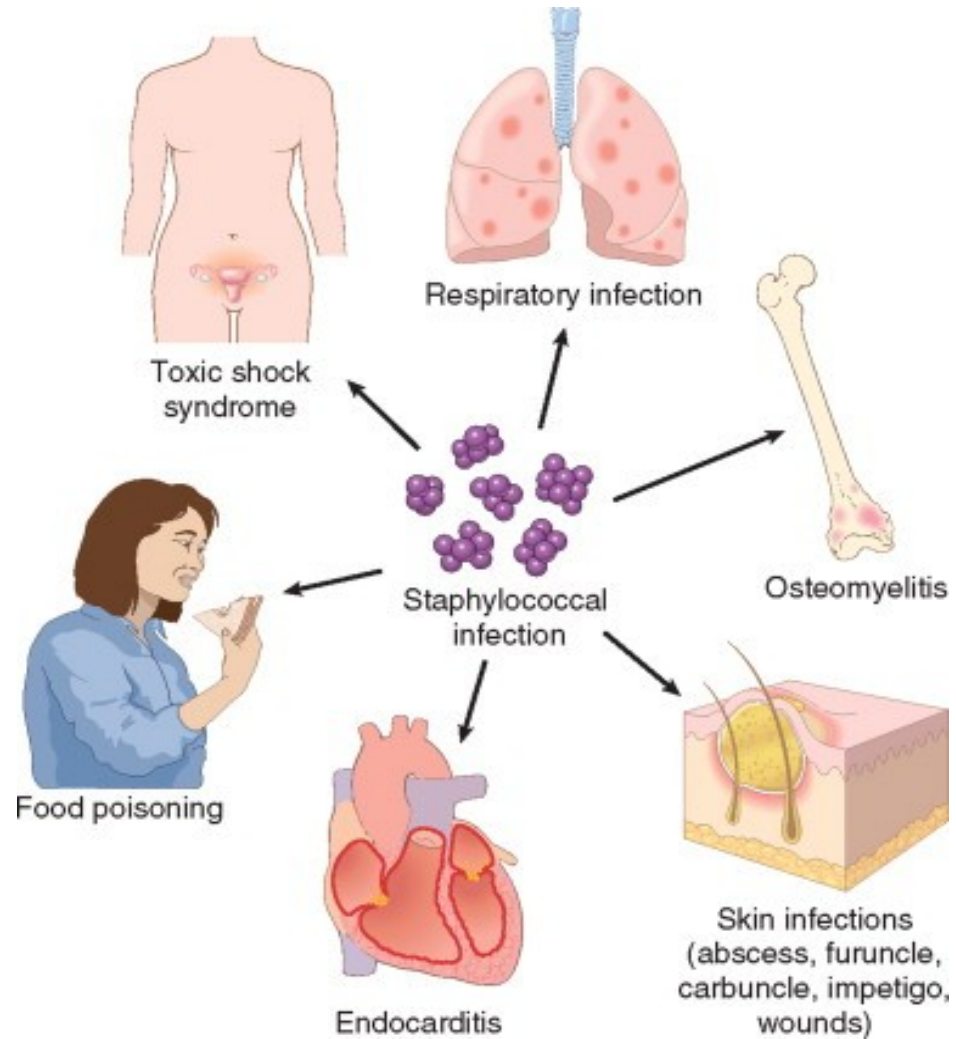
- Typical influenza

abrupt onset of systemic symptoms.

Headache, fever, chills, myalgia, or malaise, respiratory tract signs, particularly cough and sore throat.

Ocular signs and symptoms include pain on motion of the eyes, photophobia, and burning of the eye.

# Staphylococci



# Staphylococci

- Destructive pyogenic inflammation
- Abscess, furuncle, impetigo
- **Carbuncle:** deeper suppurative infection spreading laterally beneath the deep subcutaneous fascia
- **Hidradenitis:** chronic suppurative infection of apocrine glands, most often in the axilla.

# Impetigo

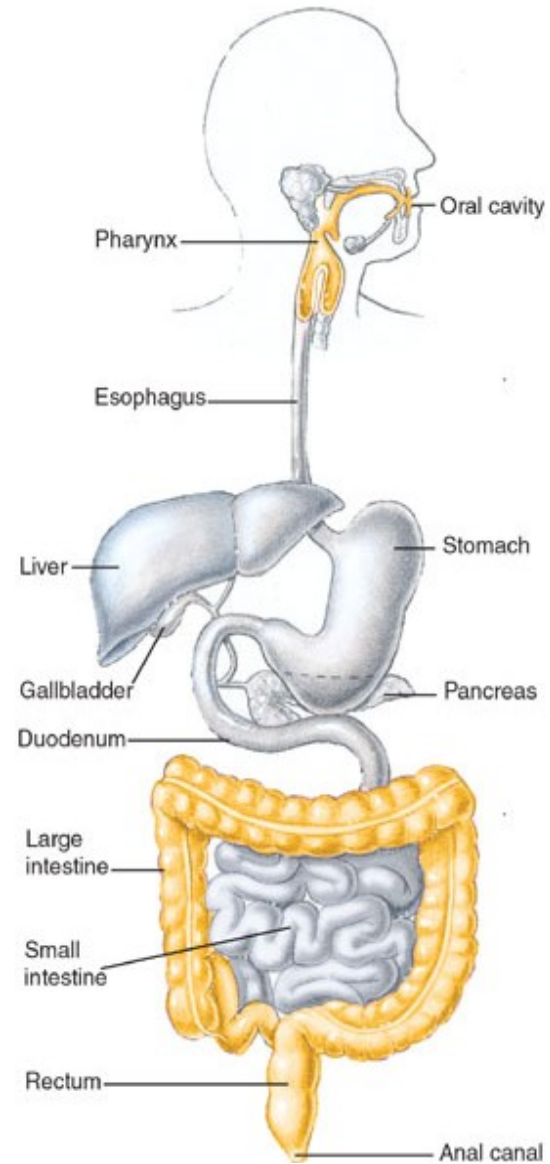


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# Streptococci

- Suppurative infections of the skin, oropharynx, lungs, heart valves.
- Post-infectious syndromes, incl. rheumatic fever, immune complex glomerulonephritis, erythema nodosum

# GIT infections



# GIT infections

- mostly by contaminated food or water
- ↓ local host defences (↓ gastric acidity, ↓ enzymatic and mucus secretion, loss of local defensins and IgA, loss of normal flora, obstruction)
- general immunodeficiency (→ fungal, CMV, MAC infection)
- resistant microorganisms (hepatitis A virus, rotavirus, H. pylori, protozoan cysts,...)

# Dental caries





# Dental caries

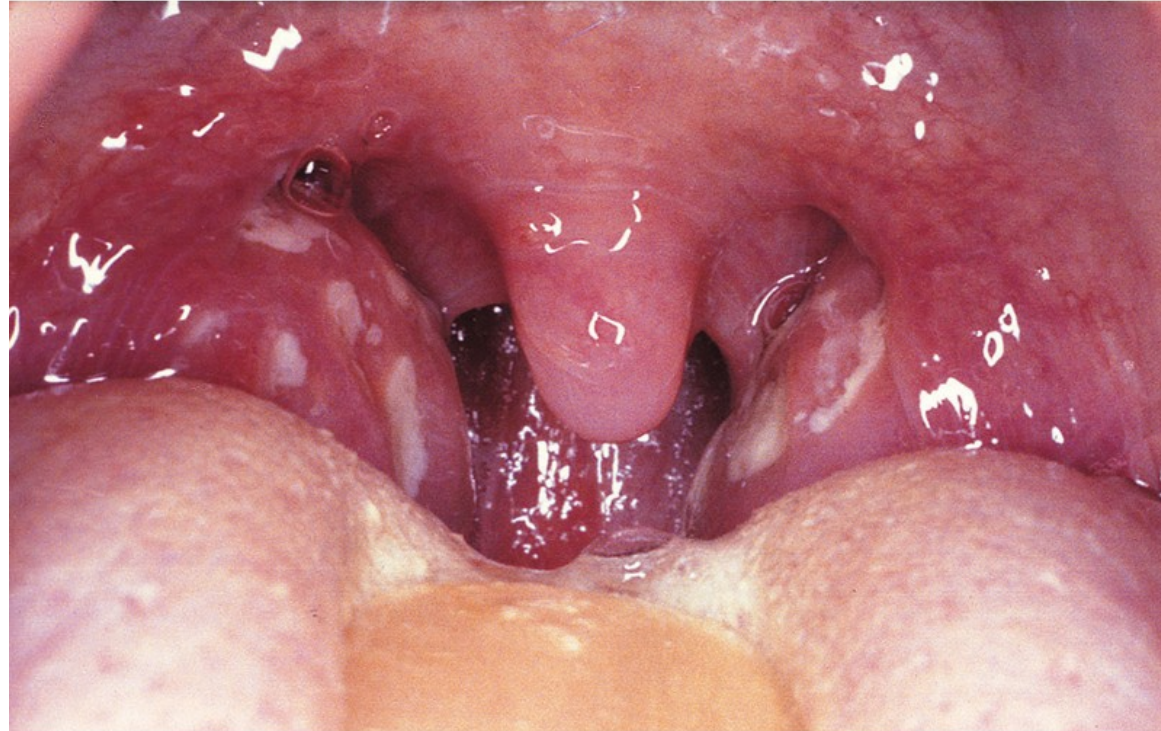
- Multifactorial dynamic process
- Involves the interaction of inborn or acquired host factors (tooth surface, saliva, acquired pellicle), diet (sugars), dental plaque (biofilm) – oral infection.
- Caries does not occur in the absence of either plaque or dietary fermentable carbohydrates.

# Tonsillitis and pharyngitis

- bacterial (Streptococcus – 25%, Staphylococcus, diphtheria...)
- viral (EBV, influenza, adenoviruses, ...)
- **Clinical** – sore throat, dysphagia, red + swollen tonsils + focal/confluent yellowish exudate, cervical lymphadenopathy, fever, malaise, ...
- In viral + rhinitis, laryngitis

# Tonsillitis

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# Intestinal infections

- **Enterocolitis** – usual manifestation as diarrhea, may be pseudomembranous, ulcerative, non-purulent
- worldwide more than 3 millions deaths annually, mainly children  $\leq 5$  yrs
- chronic or recurrent enterocolitis – parasites, protozoa

# Infectious hepatitis

- **Viral hepatitis** – part of systemic disease (EBV, CMV, yellow fever, rarely rubella, herpesvirus, etc.)
- **Viral hepatitis – liver specific** (hepatitis viruses HAV, HBV, HCV, HDV, HEV, ...)
- **Bacterial** – abscess, chronic inflammation
- **Parasitic** – abscesses, cysts - Entamoeba, Echinococcus; malaria, schistosomiasis, cryptosporidiosis, etc.
- **Fungal**

# Urogenital tract infections

- **Ascending infection** via urethra most usual (G- fecal bacteria – E. coli, Proteus,...)
- **Anatomy** – urethra 5 cm length in women, 20 cm in men
- **Predisposing factors** – obstruction, reflux, loss of protective vaginal flora, mucosal microtraumata

# Sexually Transmitted Infections

- Sexually Transmitted Disease - **STD**
- Infection transmitted through vaginal, anal or oral sex
- Every sexually active individual is at risk
- Women acquire infections from men more than men from women
- 2/3 of STD occur in people under 25 yrs of age
- Infection by multiple agents common (↑ risk)
- Fetus or infants – vertical transplacental or perinatal transmission of STD → abortus, inborn defects, neonatal infection. Diagnosis + treatment!!

# STI

- **Viruses:** HSV, HPV, HIV, hepatitis B,C
- **Chlamydiae:** Ch. trachomatis
- **Mycoplasmas:** U. urealyticum
- **Bacteria:** Neisseria gonorrhoeae (clap), Treponema pallidum (syphilis), Haemophilus ducreyi (chancroid), Klebsiella granulomatis (granuloma inguinale)
- **Protozoa:** Trichomonas vaginalis (urethritis, balanitis, vaginitis)



# Genital Warts

- Condyloma acuminatum - HPV
- Most HPV infections asymptomatic or unrecognized
- Mostly found in young, sexually active; associated with early onset of sexual activity, multiple sexual partners
- Transmitted by all types of sexual contact

# Chlamydia: Manifestations

- In women often asymptomatic until uterus and tubes infected; may present with dysuria, urinary frequency, vaginal discharge
- 1/3 of men may be asymptomatic; dysuria, urethral discharge, testicular pain
- Patient infectious even if asymptomatic

# Chlamydia: Complications

- May result in PID (pelvic inflammatory disease)
- Major cause of infertility, ectopic pregnancy in women; may cause stillbirth or spontaneous abortion (miscarriage)
- In men, may result in epididymitis, prostatitis, sterility, Reiter's syndrome
- In neonates, may cause blindness, pneumonia

# Gonorrhoea

- 'clap'; one of the most common STDs (second only to Chlamydia)
- Caused by *Neisseria gonorrhoeae*; incubation period is 2-8 days
- Transmitted by sexual contact, during passage through the birth canal
- Usually targets the cervix, male urethra

# Gonorrhoea

- Female: mostly asymptomatic until advanced disease; dysuria, urinary frequency or abnormal vaginal discharge
- Male: dysuria, serous, milky or purulent urethral discharge; regional lymphadenopathy
- Complications: prostatitis, epididymitis, sterility; PID, endometritis, salpingitis, peritonitis; in neonates gonorrhoea can infect the eyes, nose or anorectal region

# Syphilis

- Spirochete *Treponema pallidum*
- Transmitted from open lesions during sexual contact
- Organism can survive days in fluids
- May also be transmitted by infected blood, body fluids, including saliva
- Average incubation is 20-30 days
- Spreads through blood, lymphatic system
- Congenital syphilis - transplacental

# Syphilis: Primary stage

- **Chancre:** painless ulcer in the site of inoculation; regional lymphadenopathy
- chancre appears 3-4 weeks after infectious contact, disappears within 4-6 weeks
- Chancre may go unnoticed in women
- Highly infectious during primary stage even if no symptoms are present

# Syphilis: Secondary stage

- Symptoms of secondary syphilis appear any time from 2 weeks to 6 months after initial chancre disappears, in 75% of untreated people
- **Primary generalisation**, flu-like symptoms, sore throat; generalized lymphadenopathy
- **Skin rash** (especially on palms of hands and soles of feet) maculopapular, pustular;
- **condylomata lata** - mucus patches + erosions in oral cavity; flat, broad-based wart-like papules on labia, anus or corner of mouth, **highly infectious**; secondary alopecia
- Disappear within 2-6 weeks



# Syphilis - secondary



**Condylomata lata**

**Syphilitic rash**



# Skin infections

- The dense, keratinized outer layer of skin - natural barrier to infection. Low pH of the skin (5.5) and the presence of fatty acids inhibit growth of microorganisms other than residents of the normal flora.
- Potential opportunists, such as *S. epidermidis* and *Candida albicans*.
- Few microorganisms able to traverse the unbroken skin
- *Most microorganisms penetrate through breaks in the skin*

# Skin infections

- **Viral exanthematic inflammations** – HSV, varicella-zoster, etc.
- **Viral pseudotumorous lesions** – warts (HPV), molluscum contagiosum (poxvirus)
- **Bacterial infections** – superficial (impetigo – Stph. aureus, blisters + neutrophils), deep (panniculitis, phlegmona)
- **Fungal inf.** – superficial (Tinea – dermatophytes)
- **Parasitic inf.** – scabies etc.

# Fungal infections

- Superficial infections by dermatophytes : skin, hair, nails.
- The term “tinea” + the area of the body affected (e.g., tinea pedis, “athlete's foot”; tinea capitis, “ringworm of the scalp”).
- Certain fungal species invade the subcutaneous tissue, causing abscesses or granulomas (e.g., sporotrichosis and tropical mycoses).

# Common childhood viral infections

- Measles (rubeola, red measles)
- Rubella (German measles)
- *Erythema infectiosum* (Fifth disease)
- Mumps
- Varicella-Zoster (Chickenpox)
- Coxsackievirus and Echovirus associated infections (hand-foot-and-mouth disease)

# CNS infections

- Meningitis

  - acute pyogenic (bacterial)

  - aseptic (acute viral)

  - chronic (+ encephalitis; tbc, borrelia, T. pallidum, cryptococcus)

- Brain abscess (bacterial, Naegleria)

- Viral encephalitis (+ meningitis) acute (arboviruses, herpetic, CMV, poliomyelitis, rabies, HIV), persistent (progressive multifocal leukoencephalopathy – JC virus, subacute sclerosing panencephalitis – measles)

- Fungal (cryptococcus etc.), parasitic (Toxoplasma)