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FACTORS OF PATHOGENICITY AND VIRULENCE

The 7th lecture for 2nd-year students
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Pathogenicity – review

Pathogenicity = ability of a microbe to be harmful to health and to cause disease

Infectiousness = ability to cause infection

Infection – broader term than disease

In the disease symptoms of disease are present (the infection is manifest)

But the infection may proceed without symptoms (inapparent infection)

Apart from infections microbes can cause food poisoning, as well

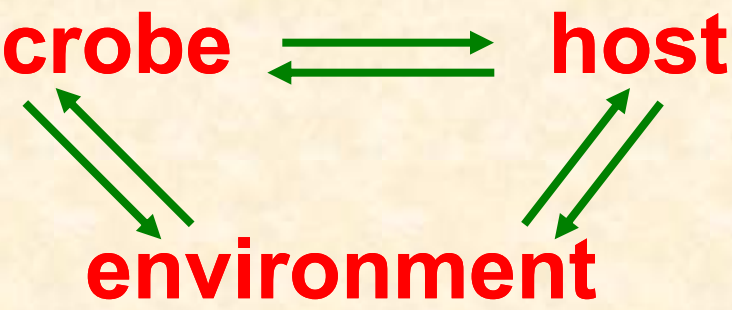
Infection – review

The definition of infection is not easy

- Infection = situation when the etiological agent of infection invades an organism and multiplies in it; or it settles on bodily surfaces and acts adversely there
- Colonization = settlement of bodily surface by a nonpathogenic microbe (or by a pathogen that does not cause pathological symptoms there)

Relationship between the microbe and the host – review

The relationship is dynamic and influenced by the environment:



Illness is not a rule – peaceful coexistence is possible – usually better for the parasite

In spite of that the host tries to get rid of the parasite – to destroy, remove or at least to localize it

Pathogenicity – review

Pathogenicity (the ability to cause a disease) depends on both species – on the microbe and on the host

Particular microbial species is pathogenic for a specific host species only, for another species it may be non-pathogenic

This host species is susceptible to the relevant microbial species, to a different microbial species it can be resistant

Primary and opportune pathogens – review

Primary (obligate) pathogens → cause disease even in otherwise healthy individuals = chiefly agents of classical infections (diphtheria, typhoid fever, plague, gonorrhea, tetanus, influenza, morbilli etc.)

Opportunistic (facultative) pathogens → cause disease under certain conditions or at a certain disposition only = usually members of normal flora

- when they reach another site in the body
- or when the immunity of the individual is lowered

Virulence – review

Virulence = degree (measure) of pathogenicity

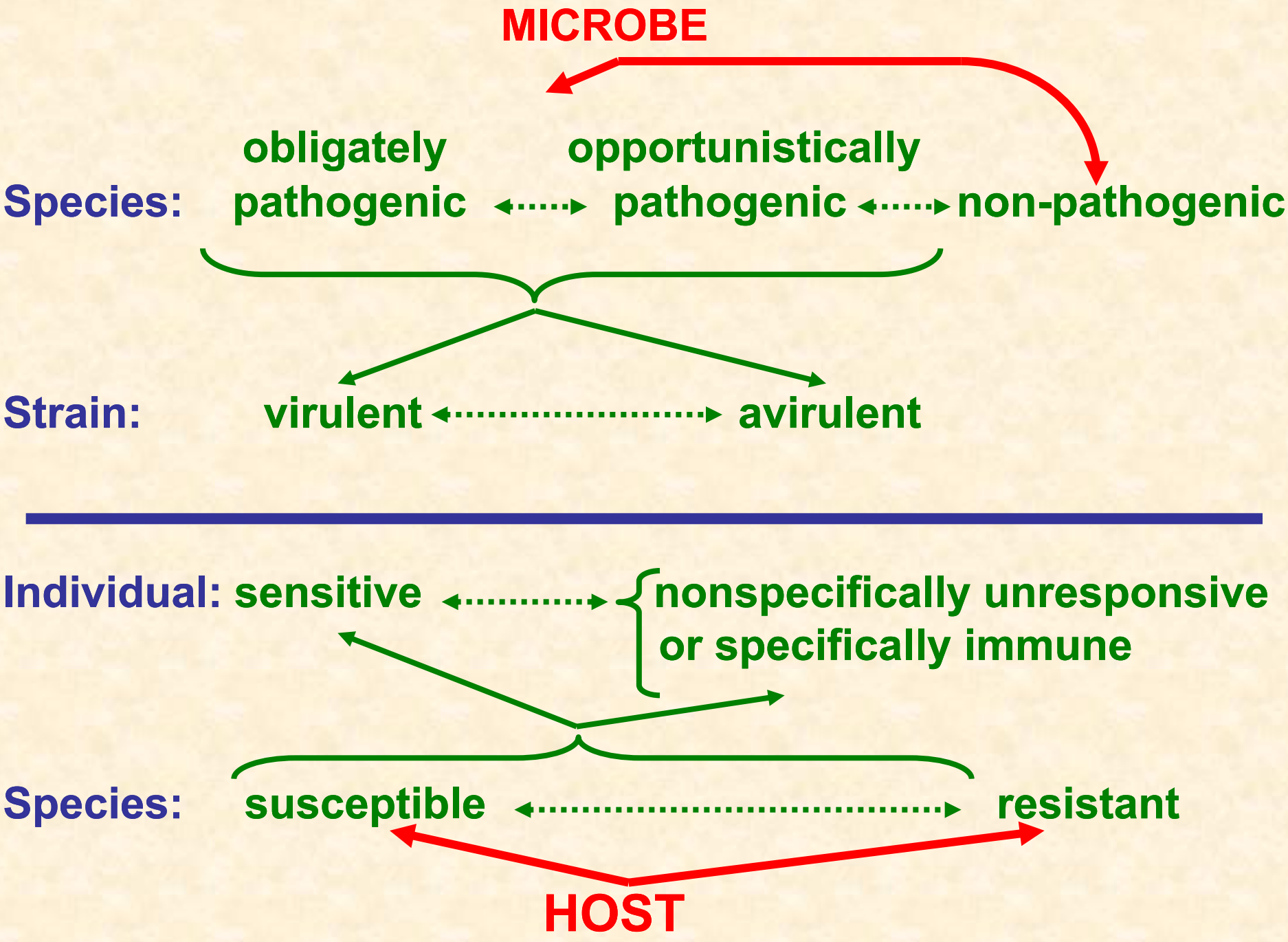
Virulence = property of certain strain – a pathogenic species can incorporate highly virulent strains as well as almost avirulent ones

Indicator of strain virulence: ability to kill

LD_{50} = 50% lethal dose (the amount of microbe that is able to kill exactly ½ of experimental animals)

Increasing virulence: repeated passages of the strain (be cautious with the strains from dissection material)

Attenuation = artificial weakening of virulence (attenuated strains serve for the preparation of vaccines)


MICROBE
obligately pathogenic
opportunistically pathogenic
non-pathogenic
Species:
Strain:
virulent
avirulent
Individual:
sensitive
nonspecifically unresponsive
or specifically immune
Species:
susceptible
resistant
HOST

Three elements of pathogenicity and virulence

1. Transmissibility (communicability) = ability to be transmitted between hosts
2. Invasiveness = ability to:
   - enter the host
   - multiply within
   - spread within

   } = { ability to overcome the defence
3. Toxicity = ability to do harm to the host

1. Transmissibility – I

It depends on

- the way of transmission – especially on
  - the way in which microbes leave the body
  - the amount of excreted microbes
  - the portal of entry into other host
- the microbe tenacity – the degree of resistance to the external environment
- the minimum infectious dose – the number of microbes required for the start of infection
- the behaviour of the host – the abuse of the host‘s defensive reflexes for the transmission

Details are taught in epidemiology

2. Invasiveness – entering the host

Most often through mucosae

Sometimes the entering is preceded by the colonization = overcoming the concurrence of commensals

Prerequisite of successful entry: ability to

- adhere to epithelium by means of *adherence factors* (e.g. fimbriae)
- penetrate through epithelium by means of *penetration factors*

Penetration into internal environment

A. Direct penetration by means of

- *small cracks in skin* (*S. aureus, Str. pyogenes, B. anthracis, Francisella tularensis,* wart viruses)
- *small cracks in mucosa* (*T. pallidum,* HBV, HIV)
- *animal bite* (rabies virus, *Pasteurella multocida*)
- *arthropod bite* (arboviruses, borreliae, plasmodia)
- *enzymes* (penetration factors: *C. perfringens* lecithinase, *S. pyogenes* hyaluronidase)

B. Forced phagocytosis

by normally non-phagocyting cells (shigellae, listeriae) compelled to phagocyte

Ability to multiply *in vivo*

- **Intracellular multiplication is better → a lot of available nutrients, defence against immunity**
  Intracellular parasites: mycobacteria, rickettsiae, chlamydiae, listeriae, salmonellae etc.
- **Extracellular multiplication – not so easy → it is obstructed by**

  - antibacterial substances in blood (complement, lysozym, antibodies)

  - high temperature (*M. leprae, M. haemophilum*)

  - but above all by shortage of free Fe (Fe is bound to lactoferin and transferin in serum)

  To get Fe bacteria produce *siderofores* and *hemolysins*

Ability to spread through the macroorganism

According the ability to spread different infections evolve:

- localized infections (common cold, salmonellosis, gonorrhoea)
- systemic infections (influenza, meningitis)
- generalized infections (morbilli, typhoid fever, exceptionally even localized and systemic infections)

Way of spreading:

by means of lymph

by means of blood

per continuitatem (into immediate neighbourhood)

along nerves

(more details will be dealt with later)

Defense against infection

Two tightly linked defense systems:

1. Innate immunity (or resistance, nonspecific one)
2. Acquired (specific, adoptive) immunity

Both systems hand in hand

a) prevent microbes from colonizing bodily surfaces

b) bar the penetration of microbes into tissues

c) inhibit their spread through the body

d) neutralize their toxins

e) aim for their liquidation and removal of their remains

Innate immunity (resistance)

Properties

- acts nonspecifically against whole microbial groups (bacteria, viruses etc.)
- is inherited, therefore it exists from the birth
- is present in all members of the given species
- is no match for obligate pathogens
- works instantly – which is extremely important!
- acts uniformly even during repeated contact

Tools

Barriers of colonization and *penetration*

Barriers of spread and *tools liquidating microbes* including *fever*

Inflammation – calor, dolor, rubor, tumor, functio laesa

Acquired immunity

Properties

- affects specifically only a particular microbe
- forms only during the lifetime after the contact with the agent
- develops only in a particular individual
- protects also against virulent strains of obligate pathogens
- starts to operate relatively late, after immune reaction has developed
- after repeated contact it acts more quickly and efficiently

Tools

Antigen-presenting cells (phagocytes)

T cells and activated macrophages (cell-mediated immunity)

B cells and producers of antibodies (humoral immunity)

Cell-mediated immunity

Indispensable against intracellular parasites (e.g. viruses, mycobacteria), which in a non-immune macroorganism remain alive and are disseminated by means of phagocytes through the body

In an immune macroorganism:

immune lymphocytes Th1 react with microbial antigens and produce cytokines, which activate macrophages

Activated macrophages go on the rampage:

1. phagocyte more vividly,
2. reliably kill engulfed microbes,
3. damage the neighboring tissue as well (delayed hypersensitivity)

In virus infections and in tumours afflicted cells are killed by *cytotoxic Tc lymphocytes*

Humoral immunity – protection by antibodies

- ***Bacterial infections:***

  support of phagocytosis – opsonization of encapsulated bacteria (IgG)

  inhibition of adherence to epithelium – mucosal antibodies IgA

  neutralization of bacterial toxins (IgG)

  bacteriolysis by complement (IgM, IgG)

  transfer of immunity across the placenta (IgG)

- ***Parasitic infections:***

  expulsion of helminths (IgE)

- ***Viral infections:***

  neutralization of virus infectivity (IgG, IgA)

How do microbes face immunity – A

A) Ability to overcome the *innate* immunity:

- Resisting complement
  inhibiting complement activation
  protecting their own surface

  Ability to resist complement → seroresistance

- Resisting phagocytosis
  avoiding being engulfed
  surviving inside the phagocyte

- Interfering with the cytokine function

Resisting phagocytosis – I

1. *Avoiding being engulfed*

inhibitors of chemotaxis (bordetellae, vaginal anaerobes, pseudomonads)

leucocidins and lecithinase (staphylococci, streptococci, pseudomonads, clostridia)

formation of capsule (the most important!)

agents of meningitis and pneumonia (*N. meningitidis, H. influenzae, E. coli, S. pneumoniae, K. pneumoniae*)

Resisting phagocytosis – II

2. Survival inside the phagocyte

blockade of phagolysosome formation
(***Chlamydia, Mycobacterium, Legionella, Toxoplasma***)

escape from phagosome
(***Rickettsia, Shigella, Listeria, Leishmania, Trypanosoma***)

production of antioxidants
(staphylococci, gonococci, meningococci)

marked tenacity
(***Coxiella, Ehrlichia***)

How do microbes face immunity – B

B) Ability to overcome the *acquired* immunity:

Always an attempt to avoid antibodies or immune lymphocytes by

- quick reproduction (respiratory viruses, diarrhoeal agents, malarial plasmodia)
- attempts to deceive immune system
  - to hide
  - to change one‘s own antigens
  - to induce tolerance
- attempts to suppress immune reaction

Ability to deceive the immune system – I

1. *To hide*
   in neural ganglions (HSV, VZV)
   on intracellular membranes (HIV, adenov.)
   in infectious focuses (*M. tbc*, echinococci)
   in privileged sites (agents of mucosal infections, *T. gondii* in eye, retroviruses in cellular genome)

2. *To induce the immune tolerance*
   (CMV, rubella v., leishmaniae, cryptococci, maybe even HIV)

Ability to deceive the immune system – II

3. *To change one's own antigens*

antigenic mimicry (*S. pyogenes, T. pallidum, M. pneumoniae*)

antigenic camouflage (schistosomes – blood proteins, staphylococci – protein A, streptococci – protein G, CMV – βmG)

antigenic variability (trypanosomes, borreliae, gonococci, influenza virus)

Ability to suppress the immune reaction

- invasion into the immune system (HIV, measles virus)
- interference in cytokine formation (*M. leprae*, protozoa)
- production of superantigens (staphylococci, streptococci)
- production of proteases (meningococci, gonococci, haemophili, pneumococci)
- binding the Fc fragment of IgG (staphylococci, streptococci, HSV)
- ? (influenza virus, HBV, EBV)

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3. Toxicity – I

Damage by *direct effect of* infectious *agent*

Cellular death

lysis by toxins, viruses, immune lymphocytes
apoptosis (HSV, shigellae)

Metabolic injury – influence of exotoxins

Mechanical causes (schistosomal eggs, *P. jirovecii*, pseudomembranes in diphtheria)

The most frequent cause of death → septic shock triggered by endotoxins

G– : lipopolysaccharide
G+ : teichoic acid + peptidoglycan

Bacterial exotoxins

Spreading factors (hyase, DNase, elastase, collagenase)

Cytolysins (lecithinase, sfingomyelinase, hemolysins)

Inhibitors of proteosynthesis (diphtheria toxin)

Pharmacologically effective toxins (choleragen, *E. coli* thermolabile enterotoxin, pertussis toxin)

Neurotoxins (tetanotoxin, botulotoxin)

Superantigens (staphylococcal enterotoxin and exfoliatin, streptococcal pyrogenic toxin)

Toxicity – II

Damage as a *result of defence reactions*

a) Injuries caused *by inflammatory reaction*:
calor, rubor, tumor, dolor, functio laesa
= typical markers of inflammation
= symptoms of disease

edema: encephalitis, epiglottitis
inflammatory infiltrate: pneumonia
suppuration: blennorrhoea neonatorum
formation of connective tissue: scarring

Toxicity – III

Damage as a *result of defence reactions*

b) Injuries caused *by specific immune reaction* (immunopathological consequences of hypersensitivity)

1st type: (IgE, anaphylaxis) helminthoses

2nd type: (cytotoxicity) hepatitis B, febris rheumat.

3rd type: (immunocomplexes) farmers lungs, poststreptococcal nephritis, systemic reactions during sepsis

4th type: (late, cellular) tbc, lepra, syphilis, actinomycosis, rash in measles

Recommended reading material

Paul de Kruif: Microbe Hunters

Paul de Kruif: Men against Death

Axel Munthe: The Story of San Michele

Sinclair Lewis: Arrowsmith

André Maurois: La vie de Sir Alexander Fleming

Michael Crichton: Andromeda Strain

Albert Camus: Peste

Please mail me other suggestions at:

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Thank you for your attention