Infective endocarditis
Methodic materials for international students (IV-VI year)

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Definition: infective endocarditis is the disease in which clinical manifestations are due to infectious inflammation of the lining of the heart chambers, heart valves, and great vessels. *Nosocomial infectious endocarditis* – manifest 48 hours after the patient is hospitalized or associated with the procedure performed within 4 weeks of the beginning of the disease, for example due to the placement of intravascular line (Swan-Ganz cagheter etc) or developing in previously damaged valve.

Prevalence

- annual incidence of 22 cases per million population in England and Wales giving rather more than 1000 cases each year; in USA – 1.7-6.2/100 000 per year
- 0.16-1.0 /1000 of hospitalizations
- men/women ratio is about 2-3:1
- in general, most common in middle-aged and over 50 (except endocarditis in i.v. drug-dependent persons)
- develops in 2-3% of patients within 1 year after prostethic valve replacement and in 0.5%/yr thereafter

There are no accurate figures, however, and this is almost certainly a considerable underestimation, particularly when a figure of 49 cases per million general population per year has been reported from the United States.

The pattern of the disease has changed considerably since antibiotics were introduced over 40 years ago:

- Once a disease mainly of young adults, there is now an increasing incidence in the over 60s, who are more likely to have degenerative valve disease such as aortic sclerosis or calcification of the mitral annulus and to be exposed to invasive investigation and therapy.
- The fall in the incidence of chronic rheumatic heart disease, which was more common in women, has resulted in a current preponderance of males with infective endocarditis.
- Overall, mitral valve prolapse is the most common underlying abnormality, with the aortic valve affected more often in elderly people. Endocarditis has also emerged as a serious complication of valve surgery and intravenous drug abuse.

Predisposing conditions:

Factors, leading to bacteriemia:

I group of factors: factors, causing transient bacteriemia

- tooth extraction
- inflammatory diseases (high-grade gingivitis – transient bacteriemia – in 10% of cases; pneumonia, puelonephritis)
- operations (oral surgery. sclerotherapu of esophagus, genitourinary and abdominal surgery)
- heart surgery: pacemaker battery replacement (risk is 6.5%); temporary transvenous pacing etc
- invasive manipulations, first of all on urogenital tract
- activities of daily living – brushing teeth etc

- i.v. narcotis use (non-sterile syringes; absence of aseptics) – direct injection of the aethiological factor to the blood

The incidence of bacteriemia after some invasive manipulations

Manipulation	Rate of bacteriemia	Microorganisms
Endoscopy	0-20%	CONS, streptococci, diphtheroids
Colonoscopy	0-20%	E.coli, bacteriodes
Barium enema	0-20%	Enterococci, aerobic and anaerobic gram-negative rods
Dental extraction	40-100%	S.viridans
Transurethral resection of prostate	20-40%	Coliforms, enterococci, S.aureus
Transesophageal echocardiography	0-20%	S.viridans, anaerobic organisms, streptococci

Factors, enhancing the colonization of microorganisms on the endothelium:

I group of factors: aethiological factors

Peculiarities of the infection:

- bacteria – 95%
- streptococcus viridans – 30-60%
- staphylococcus – 30-40%
- gram-negative bacteria (ps.aeruginosa; enterococci, HACEK-organisms (Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Kinella kingae)
- fungi
- the causing agent can't be found (mostly because of initial antibacterial treatment) – 5-25% of patients

The microorganisms that most commonly produce endocarditis have following peculiarities:

- **S. aureus:**
  - can invade the endothelial cells and increase the expression of receptors related to procoagulant activity on the cells surface
  - has increased adherence to aortic valve leaflet disks
  - inhibit the bactericidal action of complement
  - posses fibronectin receptors on the fibrin-platelet thrombus
  - causes platelet aggregation
  - resistant to platelet microbicidal proteins
  - some of the strains are also mucoid-producing
- **S.viridance**
  - inhibit the bactericidal action of complement
  - posses fibronectin receptors on the fibrin-platelet thrombus
  - has increased adherence to aortic valve leaflet disks
  - causes platelet aggregation
  - posess FimA surface adhesin
  - some of the strains are dextran-producing
- **Enterococci**
  - has increased adherence to aortic valve leaflet disks
  - posess FimA surface adhesin

Aethiological factor influence on the pattern of clinical manifestations and the course of the disease (see below).

II group of factors: preceding valves affection (affection of endothelium)

1. *Underlying valvular disease (native valve endocarditis)*

- rheumatic fever and rheumatic valve disease – less than 20%
- most significant risk factor – residual valvular changes resulting from the previous endocarditis attack
- calcific aortic stenosis – 50% of elderly patients
- congenital heart disease – 15%
- most common – bicuspid aortic valve
- in adults most common - mitral valve prolapse – 30% of cases of native valve endocarditis
- more rare – ventricular septal defects, patent ductus arteriosus, Fallot tetralogy.
- 5% of septal hypertrophy (endocarditis affecting mitral valve)

2. *Following cardiovascular surgery: endocarditis affecting primary the prosthetic structures being in contact with endocardium*

- Prosthetic valve endocarditis – 10-20%
- 5% of mechanical and bioprosthetic valves become infected (more often within 3 months after the implantation)
- Implantable pacemakers – infection of the leads in direct contact with endocardium (0.5% of the implanted pacemakers); 75% - staphylococci (both coagulaze-positive and negative)

3. *Endocarditis of previously non-affected valves (Chernogubov's variant)*

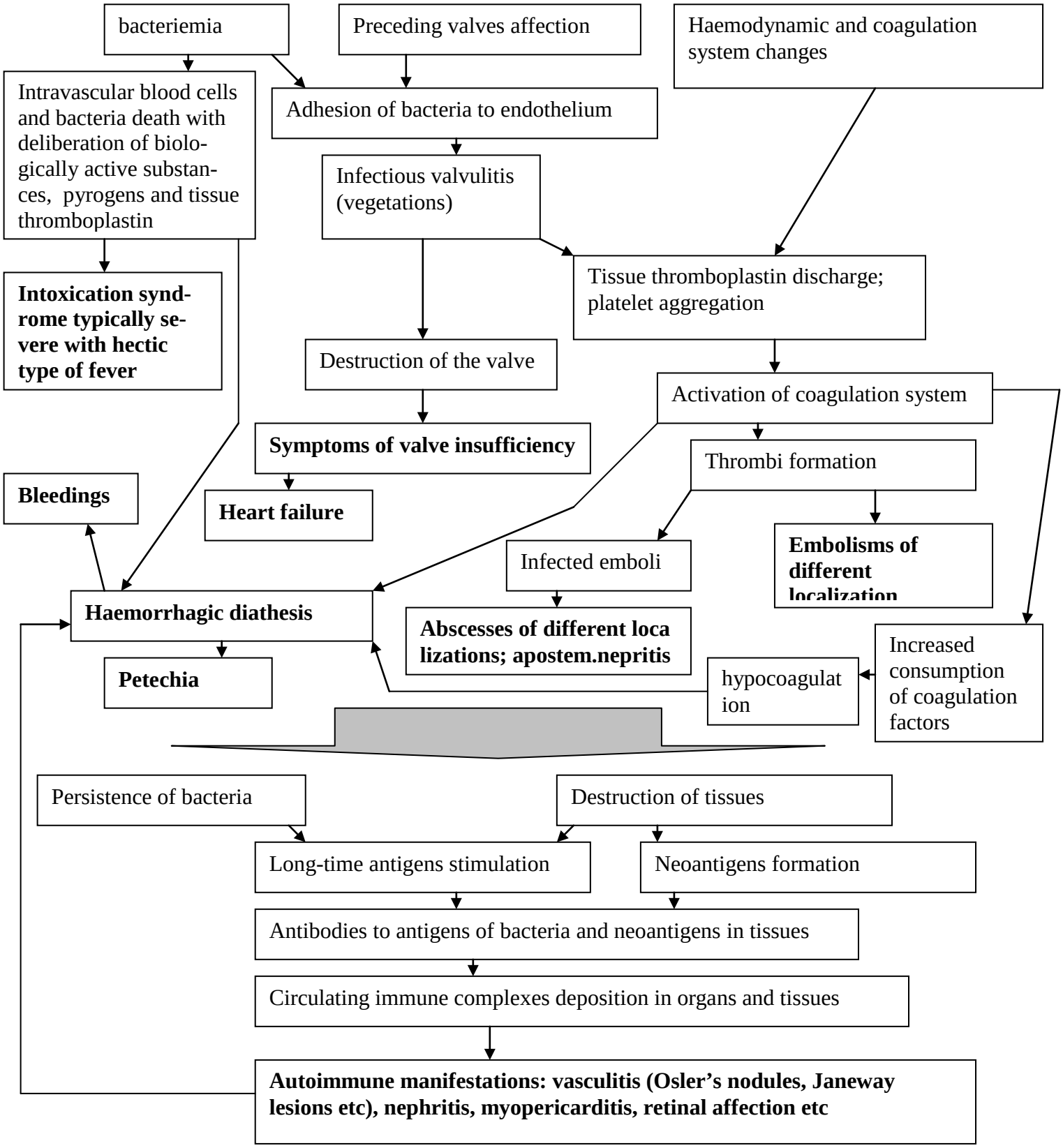
III group of factors: haemodynamics and coagulation systems peculiarities (causing endothelium affection and abacterial thrombotic endocarditis):

- gradient of pressure between the heart chambers (aortic valve, mitral valve affection; intraventricular septal defect); this leads to
- haemodynamic stress of the endothelium
- turbulent blood flow
- endothelium affection
- abacterial thrombotic endocarditis (due to the tissue thromboplastin discharge from the affected endothelium)
- general procoagulation state
- operations on heart, cathethers in heart chambers, leading to abacterial thrombotic endocarditis

IV group of factors: decrease of the anti-infection immunity

- diabetus mellitus
- cytotoxic drugs treatment
- steroids
- alcoholism
- drugs abuse

Pathogenesis of clinical syndromes



Morphology

- polip-like infected vegetations with nearby tissue necrosis, ulcerations, perforations and ruptures of valves
- abscesses in valve rings, more rare in myocardium
- vasculitis, nepritis etc – immune complexes deposition in subendothelium, mesangium with secondary proliferative-inflammatory and necrotic changes

Classification

<table>
<tr><th>Acuteness</th><th>Primary affection of cardiovascular system</th><th>aethiology</th><th>Localization</th><th>Complications</th></tr>
<tr><td>Acute</td><td>Primary (inaffected heart and large vessels</td><td rowspan="2">Bacterial
Fungal
Viral
Rickettsia</td><td>Valves: aortic, mitral, tricuspid, pulmonary</td><td rowspan="2">Heart: infarction, valve affection, pericarditis, myocarditis;
Kidneys: glomerulonephritis apostematous nephritis infarction, abscess vessels</td></tr>
<tr><td>Subacute</td><td>Secondary: valve diseases, aneurisms, anomalies of vessels, prosthetic valves, cardiomyopathies, operations on heart</td><td>Endocardium (without valves affection) endothelium of large vessels</td></tr>
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Clinical manifestations

1. *Intoxication syndrome*

- fever – in 85-92% of patient; hectic type is most common for Staphylococcus, E.coli and Ps.aeruginosa; appears 1-2 weeks after predisposing condition (tooth extraction etc)
- chills
- perspirations
- arthralgia
- myalgia
- loss of appetite

2. *Haemorrhagic diathesis*

- Petechia (conjunctivae, mucosae, skin)
- Sublingual hemorrhages
- Splinter hemorrhages under the nails
- Hemorrhagic retinal lesions (Roth's spots – round or oval lesions with small white centers)
- Subarachnoid hemorrhage from rupture of mycotic aneurism

3. *Embolisms of different localizations* (brain including transient ischemic attacks, kidneys, heart, lung, spleen etc), sometimes with development of abscesses; apostematous nephritis (multiple small abscesses of the kidney); acute septic monoarticular arthritis; purulent meningitis
4. *Auscultation signs of valve insufficiency*; sometimes acute manifestations may be present (perforation, rupture of leaflet or chorda)
5. *Heart failure* with the sings of congestion in pulmonary or/and systemic circulation
6. *Vasculitis*

- Janeway lesions irregular erythematosus painless macules (1-4 mm in diameter); most often hypothenar eminences of the hands and feet; usually represent an infectious vasculitis
- Osler nodes – smallish tender nodules that range from red to purple located in the phalanges of the fingers and toes, soles of the feet, thenar and hypothenar eminences, often preceded by neuropathic pain; last from hours to several days (non-infective vasculitis due to the immune complexes)

7. *Other autoimmune disorders*

- arthritis – usual asymmetrical with 1-3 joints affection; resembles rheumatoid arthritis, Reiter syndrome, Lyme disease; the fluid is usually sterile
- splenomegaly
- hepatomegaly (other cause - congestion)

8. Fingers and toes clubbing – in case of prolonged course

Peculiarities of the clinical manifestations and aethiological factors

Agent	Peculiarities of the clinical course
Streptococci	
Str. viridans	- 50-60% of all subacute disease - most clinical signs and symptoms are mediated immunologically
Str.intermedius group	- acute or subacute - 15% of all streptococcal cases - actively invades the tissue and leads to abscess formation
Nutritionally variant streptococci	- 5% of subacute cases - require vit B6 for growth - large vegetations, leading to embolization
Group D streptococci	- mostly subacute - 3rd most common cause of endocarditis - the source is the gastrointestinal or genitourinary tract - major problem is resistance for antibiotics
Nonenterococcal group D organisms	- subacute - concomitant diseases of the large bowel (ulcerative colitis, polyps, cancer) - sensitive to penicillin
Group B streptococci	- acute course in pregnancy and older patients - mortality rate is 40% - complications include metastatic infections, arterial thrombi, congestive heart failure - often requires valve replacement for cure
Group A,C,G streptococci	- acute disease resembles that of S.aureus - mortality rate is 30-70% - group A respond to penicillin - group C and G require a combination of synergistic antibiotics
Staphylococci	
S.aureus	- most common case of subacute, acute, prosthetic valve endocarditis, intravenous drugs abuse endocarditis; second (after coagulase-negative form) cause of nosocomial endocarditis - 35-60.5% of bacteriemias are complicated by endocarditis - more than 50% of cases are without preceding valve disorders - mortality rate is 40-50% - 50% - methicillin resistance - the primary risk factor is intravascular lines; also risk factors are diabetes, steroids, drugs abuse, alcoholism, renal failure
Coagulase-negative S.aureus	- subacute - resembles S.viridans infection
Others	
Pseudomonas aeruginosa	- usually acute, except if involves the right side of heart in i.v. drug dependent - surgery is commonly required for cure
HACEK	- usually subacute

	- 5% of all cases; most common gram-negative causes - complications include massive arterial emboli and congestive heart failure
Bartinella	- the most common is Bartonella quintana - usually in homeless males with extremely substandard hygiene
Polymicrobal	- the most common combination is Pseudomonas and enterococci - usually in i.v. drug-dependent persons - cardiac surgery mortality rate is twice that associated with single-agent endocarditis
Fungi	
Fungi	- most frequently subacute - most common is Candida albicans (prosthetic valves usually) - i.v. drugs dependent - usually Candida parapsilosis or Candida tropicalis - Aspergillus are observed in prosthetic valves endocarditis and nosocomial endocarditis - large vegetations - large arterial embols - rapid destruction of the valve

Laboratory tests:

- normochromous anaemia; normal/elevated WBC with shift to the left (sometimes up to myelocytes – leucemoid reaction); increased ESR
- Inflammatory changes in blood biochemistry – CRP, increased fibrinogen, alpha-2- and gamma-globulins
- Autoimmunity markers – rheumatoid factor, circulating immune complexes, decrease of complement, sometimes positive Wasserman's reaction
- Bacteriemia

Test is better to be taken before the start of antibacterial treatment (but it is impossible to delay treatment if blood samples for bacteriological investigation can't be taken immediately):

- from different veins
- 10-15 ml 3-5 times with the interval no less than 15 minutes in acute and 4-6 hours in subacute course
- blood should be taken for different mediums
- negative results are obtained in 20-35% (analysis taken in case of antibacterial treatment, fungal, viral endocarditis)
- urine analysis: glomerulonephritis
- echocardiography – the most informative
- most informative is transesophagal, revealing vegetations no less than 5 mm.
- vegetations appear usually 2 weeks after the onset of the disease and remain several months after it is cured
- echocardiographic predictors of systemic embolization are large valvular vegetations; mobile but predunculated vegetations, noncalcified vegetations
- ultrasonic investigation of the abdomen – hepatomegaly, splenomegaly, abscesses if present
- radionuclinde scan – to reveal splenic abscesses
- CT scan – in case of CNS symtoms

Criteria for diagnosis

I.

Confirmed – presence of all the signs:

- fever
- murmur in the heart (especially appearance or changes of preexisting murmur)
- embolisms
- bacteriemia
- vegetations

Probable:

- absence of vegetations; other sings are present

Possible only 2-3 signs are present:

- fever of unknown aethiology
- embolisms
- or/and murmur

II. Durack criteria:

- Major blood culture criteria

* 2 blood cultures positive for organisms typically found in endocarditis – S.viridans, S.aureus, enterococci in the absence of a primary focus
* 3 or more separate blood cultures drawn at least 1 hour apart

- Major echocardiographic criteria

* oscillating intracardiac mass on a valve or on implanted material in absence of alternative anatomical explanation
* myocardial abscess
* development of partial dehiscence of a prosthetic valve
* new-onset valvular regurgitation

- Minor croteria

* predisposing heart condition or i.v. drug use
* fever 38o C or higher
* vascular phen0omenon, including major arterial emboli, septic pulmonary infarctions, mycotic aneurism hemorrhage, Janeway lesions
* autoimmune disorders – Osler nodes, Roth spots, glomerulonephritis etc
* positive blood cultures not meeting major criteria or serological evidences of active infection of Coxiella burnetti (Q-fever), Legionella etc
* echographic results consistent with endocarditis but not meeting major criterla

Rejection criteria

- presemce of firm alternative diagnosis of the manifestations of endocarditis
- resolution of manifestations after 4 or fewer days of antibacterial treatment
- no evidences at surgery or autopsy after 4 or less days of antimicrobial theraphy

Diagnostic formula

- primary or secondary
- aethiology
- preexisting disease
- localization and complications

Examples:

1. Primary infectious endocarditis, caused by Str.viridans. Aortic insufficiency
2. Secondary infectious endocarditis of the mitral valve. Combined mitral-aortic valve affection due to chronic rheumatic valve disease. Embol-caused myocardial infarction (date). Congestive heart failure III functional class NYHA.

Differential diagnosis

- in rheumatic patients – exacerbation

- autoimmune diseases
- malignant neoplasms
- lymphomas and other blood-related malignancies

Course:

Acute endocarditis

Manifestations are mostly the same but the course is more rapid and without autoimmune disorders; rapid valvular destruction, valve ring abscesses, septic emboli, septic shock.

Prosthetic valve endocarditis

Valve ring abscesses, obstructing vegetations, myocardial abscesses, mycotic aneurisms manifested by valve obstruction and condiction disturbances

Right-sided endocarditis (usually in i.v. drug-dependent persons)

Septic phlebitis, fever, pleurisy, hemopthysis, septic pulmonary infarctions (multiple), affection of tricuspid or pulmonary valves

In aged with congestive heart failure – usually masked clinical manifestations

Prognosis and outcomes

- in absence of treatment – fatal
- mortality rate depends on the infection: Str.viridans – 10%; Aspergillus – about 100%; cardiac surgery improves the survival
- poor prognosis is associated with:
- heart failure
- old age
- aortic or multiple valve involvement
- large vegetations
- polymicrobal bacteremia
- resistance to antibiotics
- delay in initiating therapy
- mycotic aneurisms
- valve ring abscessis
- major embolic events
- causes of death are embols, heart failure, bacterial shock
- high risk of relapses is present; so repeated blood cultures should be taken in 2-6 weeks after cessation of antibiotics

Treatment

The initial treatment is based on the fact that usual cause is streptococci

Recommendation for antibiotics treatment