INFECTIVE ENDOCARDITIS

V. N. KARAZIN KHARKIV NATIONAL UNIVERSITY
INTERNAL MEDICINE DEPARTMENT

Performed: student of V course, gr. 527 Manish Kumar

Scientific advisers: ass.prof Makharynska O.S., ass.prof Guravka N.V.

Head of department: prof. Yabluchansky M.I.
GOALS

• Recognize the risk factors, signs, and symptoms of infectious endocarditis
• Understand the many approaches to diagnosing infectious endocarditis
• Appreciate the necessity of rapid treatment
• Anticipate possible complications
DEFINITION

• Infective endocarditis (IE) - a microbial infection of the heart valves (native or prosthetic), the lining of a cardiac chamber or blood vessel, or a congenital anomaly (e.g. septal defect)

• The valves of the heart do not receive any dedicated blood supply

• As a result, defensive immune mechanisms (such as white blood cells) cannot directly reach the valves via the bloodstream
EPIDEMIOLOGY

• Epidemiology Incidence difficult to ascertain and varies according to location
• Much more common in males than in females
• May occur in persons of any age and increasingly common in elderly
• Mortality ranges from 20-30 %
• In developed countries, the incidence of endocarditis ranges from 4 to 7 cases per 100,000 population per year and has remained relatively stable during recent decades
• The incidence of IE involving cardiovascular implanted devices, primarily permanent pacemakers and implanted cardioverter-defibrillators ranges from 0.5 to 1.14 cases per 1000 device recipients and is higher among patients with an implantable cardioverter-defibrillator than among those with a permanent pacemaker
IMPORTANT RISK FACTORS

Some of the most important risk factors include:

✓ Presence of a prosthetic valve (highest risk)
✓ Previous endocarditis (highest risk)
✓ Complex cyanotic congenital heart disease (e.g., single ventricle states)
✓ Surgically constructed systemic pulmonary shunts or conduits
✓ Acquired valvular dysfunction (e.g., rheumatic heart disease)
✓ Hypertrophic cardiomyopathy
✓ Mitral valve prolapse with regurgitation
✓ IV drug abuse Important Risk Factors
OUR PATIENT

• Patient K.O.N.
• 24 y. old
• unemployed
• city resident
• Date of admission: 05 – September – 2015
COMPLAINTS

- dyspnea
- impossibility of deep inhale
- increasing of body temperature till 38°C
- palpitation
- edemas of low extremities
- icteric skin color
ANAMNESIS MORBI

- 10 days before admission patient felt bad, appeared high body temperature till 39°C, yellowish color of skin, palpitation

- previously was drug addict (IV drugs injections)

- was delivered by ambulance in therapy department after infectious diseases specialist consultation: Community – acquired 2-sided pneumonia. Chronic toxic hepatitis. Secondary enteropathy. Sepsis?
ANAMNESIS VITAE

- Childhood infections, injuries, tuberculosis, sexually transmitted diseases were denied
- Appendectomy - 2013
- Hereditary diseases are not identified
- Allergic history is not burdened
- Smoker during 5 years, do not abuse alcohol
OBJECTIVE STATUS

- Conciseness - clear, state - severe, body position - lying on his back
- Patient can orientate himself in place, time, his personality
- Yellowish skin and mucosae, herpes labialis
- Thyroid: no pathological changes
- Skeleto – muscular system - no pathological changes
- BR – 24-26 /min, Sp O2 – 91-92%
- Lung percussion: dullness below scapula angles from both sides
- Lung auscultation: weak breathing, whizzing in upper parts, crepitation – lower parts 2-sided
- Borders of the heart: right border – outside of midsternal right line on 2 cm
- Heart auscultation: rhythmic, heart tones – muffled, systolic murmur in IV point
- Pulse – rhythmic, 120 bts/min
- BP 80 / 40 mm Hg
- Abdomen: normal size, symmetric, pain during palpation in right hypochondrium
- Liver: liver margin is 3 cm below right rib cage
- Spleen: normal
- Pasternatsky symptom – negative from both sides
- Edemas: calves and feet
- Varicose vein disease of lower extremities – absent
- Stool: liquid, 2-3 times, dark color
PRELIMINARY DIAGNOSIS OF ADMISSION WARD PHYSICIAN

Community-acquired 2-sided pneumonia. RF II stage. Toxic chronic hepatitis. Sepsis?
SURVEY PLAN

• BC and urine analysis
• Electrolytes
• Liver function tests
• Serology (markers of hepatitis)
• Ultrasound of heart, liver, kidneys
• ECG
• CFC-NAC, rheumatic factor
• Blood culture
• Chest X-ray
• Sputum analysis
• RW and AIDS – tests (on patient’s agreement)
In the middle and lower parts of left lung can be seen transparency decreasing due to infiltration. Right lung – in the middle region can be seen focal areas of infiltration. Diaphragm's cupulas are flattened. Sinuses are poorly differentiated. Flat waist of heart. Right heart border is increased. Elongation of aorta.

**Conclusion:** 2-sided pneumonia
Conclusion: sinus tachycardia
EF – 60% (N - 55 – 78%).
On anterior leaflet of tricuspid valve is present a high density vegetation on narrow base – 14mm. On septal leaflets – 6 mm high density vegetation on wide basement.

**Conclusion:** Dilatation of the right heart chambers. Infective endocarditis with involvement of tricuspid valve. Tricuspid regurgitation 3\(^{rd}\) degree. Right sided nephroptosis. 2- sided hydrocalicosis.
## BLOOD COUNT

<table>
<thead>
<tr>
<th></th>
<th>05/09/15</th>
<th>22 / 09 / 2015</th>
<th>25 / 09 / 2015 After blood transfusion</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/l</td>
<td>110</td>
<td>37</td>
<td>53</td>
<td>130 – 160</td>
</tr>
<tr>
<td>Red blood cells, 10^12</td>
<td>3.6</td>
<td>1.4 poikilocytosis</td>
<td>2.3 microcytosis, poikilocytosis</td>
<td>4.0 – 5.0</td>
</tr>
<tr>
<td>Color index of blood</td>
<td>0.9</td>
<td>0.79</td>
<td>0.79</td>
<td>0.85 – 1.15</td>
</tr>
<tr>
<td>Platelets, 10^9</td>
<td>240</td>
<td>256</td>
<td></td>
<td>180 - 320</td>
</tr>
<tr>
<td>White blood cells, 10^9</td>
<td>12</td>
<td>4</td>
<td>5.2</td>
<td>4 - 9</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>15</td>
<td>82</td>
<td>65</td>
<td>1 - 10</td>
</tr>
<tr>
<td>Bands</td>
<td>1</td>
<td>7%</td>
<td>4%</td>
<td>1.06 – 6%</td>
</tr>
<tr>
<td>Segments</td>
<td>4</td>
<td>78%</td>
<td>69%</td>
<td>47 – 72%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>69</td>
<td>1%</td>
<td>2%</td>
<td>0.5 – 5%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>6</td>
<td>3%</td>
<td>9%</td>
<td>0.1 – 3%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>20</td>
<td>11%</td>
<td>16%</td>
<td>19 – 37 %</td>
</tr>
</tbody>
</table>

Conclusion: hypochromic anaemia 3rd degree, stab shift on the left, lymphocytosis (05/09/15)
## BIOCHEMISTRY TEST DATA from 12/09/15

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient’s ranges,</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin, mmol/l</td>
<td>25</td>
<td>3 - 17</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>63</td>
<td>&lt; 37</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>52</td>
<td>&lt; 41</td>
</tr>
<tr>
<td>Rheumatoid factor, IU/l</td>
<td>17.9</td>
<td>till 30</td>
</tr>
<tr>
<td>CFK-NAC, U/l</td>
<td>39</td>
<td>38-174</td>
</tr>
<tr>
<td>HBsAg</td>
<td>0.008 (negat)</td>
<td>till 0.072</td>
</tr>
<tr>
<td>Anti- HCV</td>
<td>0.712</td>
<td>till 0.316</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.5</td>
<td>3.9 – 6.4</td>
</tr>
<tr>
<td>Total protein, g/l</td>
<td>61</td>
<td>65-85</td>
</tr>
<tr>
<td>Urea, mmol/l</td>
<td>20.8</td>
<td>2.5 – 8.3</td>
</tr>
<tr>
<td>Ag p24 /Anti – HIV Ab</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>RW</td>
<td>negative</td>
<td>negative</td>
</tr>
</tbody>
</table>

Conclusion: hepatitis C, low activity
## URINE TEST from 26/09/15

<table>
<thead>
<tr>
<th>Patient’s ranges</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>ρ 1.009</td>
<td>1.001 – 1.040</td>
</tr>
<tr>
<td>glucose -</td>
<td>-</td>
</tr>
<tr>
<td>protein 0.216 g/l</td>
<td>-</td>
</tr>
<tr>
<td>leukocytes 25-30</td>
<td>1-2</td>
</tr>
<tr>
<td>hyaline casts 1-2</td>
<td>-</td>
</tr>
<tr>
<td>granular casts 1-2</td>
<td>-</td>
</tr>
<tr>
<td>pH 6.0</td>
<td>5-7</td>
</tr>
</tbody>
</table>

Conclusion: Leukocyturea, proteinurea
BLOOD CULTURE

- From 12/09/2015 #40 – sterile (negative)
- From 27/09/2015 #86 – sterile (negative)

Patients has culture-negative Infective endocarditis
Conclusion: Acute infectious endocarditis of IV drug users, culture – negative, right - sided, primary affection of tricuspid valve

Recommendations: continue antibacterial treatment, routine surgical intervention in V.T. Zaycev Institution of general and urgent surgery NAMS of Ukraine
HEART ULTRASOUND from 01/10/2015:

EF (ejection fraction) – 68% (N: 55 – 78%)
FS (function of shortening) – 31% (N: 28 – 44%)
Mitral valve: no changes
Aortic valve: no changes
Tricuspid valves: multiple vegetations. Reversed blood flow 3+
Pulmonary trunk valve: no changes
Left ventricle:
Final diastolic size of LV cavity - 4.6 cm (N)
Final systolic size of LV cavity – 2.8 cm (N)
Left ventricle wall hypertrophy. Intraventricular septum size – 1.5 cm
Final diastolic volume of LV cavity – 100 ml (N)
Final systolic volume of LV cavity – 31 ml (N)
Stroke volume – 68 ml (N)
Right ventricle: Increased cavity size
Right atrium: enlarged (diameter – 4.3 cm)
Left atrium: not enlarged

Conclusion: No akinesia zones. Multiple vegetations on tricuspid valve. Tricuspid regurgitation 3rd degree. Dilatation of the right heart chambers. Hypertrophy of LV.
The clinical diagnosis according to current classifications
European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis.

### Clinical suspicion of IE

- **Definite IE**
- **Possible/rejected IE but high suspicion**
- **Rejected IE Low suspicion**

#### Native valve

1. Repeat echo (TTE + TOE)/microbiology
2. Imaging for embolic events*
3. Cardiac CT

#### Prosthetic valve

1. Repeat echo (TTE + TOE)/microbiology
2. 18F-FDG PET/CT or Leucocytes labeled SPECT/CT
3. Cardiac CT
4. Imaging for embolic events*

#### ESC 2015 modified diagnostic criteria

- **Definite IE**
- **Possible IE**
- **Rejected IE**

---

### Definition of IE According to the Modified Duke Criteria*

#### Definite IE

**Pathological criteria**

Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis.

**Clinical criteria**

2 Major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria

#### Possible IE

1 Major criterion and 1 minor criterion, or 3 minor criteria

#### Rejected

Firm alternative diagnosis explaining evidence of IE; or resolution of IE syndrome with antibiotic therapy for ≤4 d; or no pathological evidence of IE at surgery or autopsy with antibiotic therapy for ≤4 d; or does not meet criteria for possible IE as above

IE indicates infective endocarditis.

---

CT = computed tomography; FDG = fluorodeoxyglucose; IE = infective endocarditis; PET = positron emission tomography; SPECT = single photon emission computerized tomography; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography.

*May include cerebral MRI, whole body CT, and/or PET/CT.
Major Diagnostic Criteria

- Positive blood culture for typical Infective Endocarditis organisms (strep viridins or bovis, HACEK, staph aureus without other primary site, enterococcus), from 2 separate blood cultures or 2 positive cultures from samples drawn > 12 hours apart, or 3 or a majority of 4 separate cultures of blood (first and last sample drawn 1 hour apart)
- Echocardiogram with oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or abscess, or new partial dehiscence of prosthetic valve or new valvular regurgitation

Minor Diagnostic Criteria

- Predisposing heart condition or intravenous drug use
- Temp > 38.0° C (100.4° F)
- Vascular phenomena: arterial emboli, pulmonary infarcts, mycotic aneurysms, intracranial bleed, conjunctival hemorrhages, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with endocarditis (excluding coag neg staph, and other common contaminants)
- Echocardiographic findings: consistent with endocarditis but do not meet a major criterion as noted above
CLASSIFICATION BY DURATION

**Acute endocarditis** is a hectically febrile illness that rapidly damages cardiac structures, seeds extracardiac sites, and, if untreated, progresses to death within weeks.

- a fulminant illness
- associated with high fevers, systemic toxicity,
- is more likely due to *Staphylococcus aureus*
- which has much greater virulence, or disease-producing capacity and frequently causes metastatic infection
- Affects normal heart valves

**Subacute endocarditis** follows an indolent course; causes structural cardiac damage only slowly, if at all; rarely metastasizes; and is gradually progressive unless complicated by a major embolic event or a ruptured mycotic aneurysm

- low virulence and
- mild to moderate illness
- usually occurring in a setting of prior valvular heart disease
- If not treated, usually fatal by one year
- often due to streptococci

**OUR PATIENTS HAS ACUTE FORM OF INFECTIVE ENDOCARDITIS**
CLASSIFICATION BY HEART- SIDE INVOLVEMENT

Left-sided valve infective endocarditis

- Surgical treatment is required in approximately half of the patients with IE because of severe complications
- HF is the most frequent complication of IE
- Uncontrolled infection is one of the most feared complications of IE and is the second most frequent cause for surgery
- Embolic events are a frequent and life-threatening complication of IE related to the migration of cardiac vegetations. The brain and spleen are the most frequent sites of embolism in left-sided IE

Right-sided infective endocarditis

(our patient)

- Right-sided IE accounts for 5–10% of IE cases.
- Although it may occur in patients with a pacemaker, ICD, central venous catheter or CHD, this situation is most frequently observed in IVDAs, especially in patients with concomitant human immunodeficiency virus (HIV) seropositivity or in immunosuppressed patients
- S. aureus is the predominant organism (60–90% of cases), with methicillin-resistant strains becoming more prevalent. Pulmonary embolism is frequent in native right-sided IE
CLASSIFICATION BY CULTURE RESULTS

IE can be culture-positive or culture-negative

• By far the most common cause of a "culture-negative" endocarditis is prior administration of antibiotics

• Sometimes micro-organisms can take a longer period of time to grow in the culture media, such organisms are said to be fastidious because they have demanding growth requirements

• Some examples include pathogens like Aspergillus species, Brucella species, Coxiella burnetii, Chlamydia species, and HACEK bacteria

OUR PATIENT: Blood culture - negative
HACEK BACTERIA

- **HACEK** organisms are a group of bacteria that live on the dental gums, and can be seen with IV drug users who contaminate their needles with saliva. Patients may also have a history of poor dental hygiene, or pre-existing valvular disease.

- **HAEMOPILLUS**
- **ACTINOBACILLUS**
- **CARDIOBACTERIUM HOMINIS**
- **EIKENELLA**
- **KINGELLA KINGAE**
# Epidemiological Clues That May be Helpful in Defining the Etiological Diagnosis of Culture-Negative Endocarditis

<table>
<thead>
<tr>
<th>Epidemiological Feature</th>
<th>Common Microorganism</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDU</td>
<td><em>S. aureus</em>, including community-acquired oxacillin-resistant strains</td>
</tr>
<tr>
<td></td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td></td>
<td>β-Hemolytic streptococci</td>
</tr>
<tr>
<td></td>
<td>Fungi</td>
</tr>
<tr>
<td></td>
<td>Aerobic Gram-negative bacilli, including <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td>Polymicrobial</td>
</tr>
<tr>
<td>AIDS</td>
<td><em>Salmonella sp</em></td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Pneumonia, meningitis</td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td><em>S. pneumoniae</em></td>
</tr>
</tbody>
</table>

*Circulation*. 2015;132:00-00. DOI: 10.1161/CIR.0000000000000296
CLASSIFICATION BY VALVE TYPE

native-valve endocarditis or prosthetic-valve endocarditis
(as in our patient case)

• Prosthetic valve endocarditis can be
  • early (< 60 days of valvular surgery),
  • intermediate (60 days to 1 year) or
  • late (> 1 year following valvular surgery)
• Early prosthetic valve endocarditis arising within 2 months of valve surgery is generally nosocomial, the result of intraoperative contamination of the prosthesis or a bacteremic postoperative complication. This nosocomial origin is reflected in the primary microbial causes: S. aureus, CoNS, facultative gram-negative bacilli, diphtheroids, and fungi
• PVE that presents 2—12 months after surgery often represents delayed-onset nosocomial infection
• Late prosthetic valve endocarditis beginning > 12 months after surgery is usually due to community acquired microorganisms
OTHER CLASSIFICATION APPROACHES

• Other Classification Approaches Classified into 4 groups:
  • Native Valve IE
  • Prosthetic Valve IE
  • Intravenous drug abuse (IVDA) IE – our patient
  • Nosocomial IE
<table>
<thead>
<tr>
<th>Functional Class</th>
<th>Patients symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>III</td>
<td><strong>Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea</strong></td>
</tr>
<tr>
<td>IV</td>
<td>Enable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class</th>
<th>Objective assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.</td>
</tr>
<tr>
<td>C</td>
<td><strong>Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.</strong></td>
</tr>
<tr>
<td>D</td>
<td>Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.</td>
</tr>
</tbody>
</table>
PNEUMONIA CLASSIFICATION

1. **Community-acquired pneumonia (CAP)** is that which occurs in the absence of immune compromise or prior hospital admission within the previous 30 days.

2. Hospital-acquired pneumonia (HAP) or nosocomial pneumonia can occur in anyone resident in hospital for > 48 h.

3. **Ventilator-associated pneumonia (VAP)** hospital - common in the intensive care unit > 48 h after endotracheal intubation

4. Pneumonia in the immunocompromised

5. Aspiration pneumonia – in those with swallowing impairment and neurological impairment
CURB - 65 SCALE OF PNEUMONIA SEVERITY

C: mental confusion
U: blood urea > 7 mmol/l (patient 20.8 mmol/l)
R: respiratory rate ≥ 30 breaths in min
B: systolic blood pressure < 90 mmHg or (patient BP – 80/40) diastolic blood pressure ≤ 60 mmHg
65: age ≥ 65 years

Mild pneumonia: score of 0–1 (mortality 1.5%)
Moderate pneumonia: score of 2 (9%)
Severe pneumonia: score of 3–5 (22%)
BY Mean Cell Hemoglobin (represents the average content of Hb in average RBC):

I. Hypochromic anemia < 27 picograms/cell
II. Hyperchromic anemia > 31 picograms/cell
III. Normochromic anemia 27 - 31 picograms/cell

Classification of anemia according to the degree of severity

1. Mild - hemoglobin - 120-90 g/l
2. Moderate - hemoglobin - 90-70 g/l
3. Severe - hemoglobin - less than 70 g/l
**DOES THIS PATIENT HAS SEPSIS?**

Sepsis: when SIRS is present in an individual patient and the cause is thought likely to be an infection (definitive or suspected source), sepsis is present.

**The clinical criteria for the Systemic Inflammatory Response Syndrome (SIRS)**

SIRS is defined by the presence of 2 or more criteria from a collection of clinical signs and laboratory investigations as follows:

- **Temperature** >38.3°C (101°F) or <36.0°C (96.8°F)
- **Tachycardia** >90 bpm
- **Tachypnoea** >20 breaths/minute
- **PCO₂** <4.3 kPa (32 mmHg)
- **Hyperglycaemia** (blood glucose >6.66 mmol/L [120 mg/dL]) in absence of diabetes mellitus
- **Acutely altered mental status**
- **WBC count** >12×10^9/L (12,000/microlitre) or <4×10^9/L (4000/microlitre), or normal WBC count with >10% immature forms.

http://bestpractice.bmj.com/best-practice/monograph/245/diagnosis/criteria.html
COMPLETE DIAGNOSIS of our patient is:

Main:
Acute infectious endocarditis of IV drug users, culture – negative, right-sided, primary affection of tricuspid valve, target organs (heart, lungs)

Complications:
Congestive Heart Failure with preserved left ventricular pump function (ejection fraction = 60%), III C functional class by NYHA
Community-acquired 2-sided pneumonia, moderate. RF II stage.
Hypochromic anemia 3rd stage

Concomitant disease:
Chronic C hepatitis with minimal activity.
TREATMENT

DESIRED OUTCOME:

• **Relieve** the signs and symptoms of disease

• **Decrease** morbidity and mortality associated

• **Eradicate** the causative organism with minimal drug exposure

• **Provide** cost-effective antimicrobial therapy

• **Prevent** IE in high-risk patients with appropriate prophylactic antimicrobials
GENERAL PRINCIPLES

- The most important approach to treatment of IE includes isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by high-dose antibiotics.
- Treatment usually is started in the hospital, but in selected patients, it may be completed in the outpatient setting.
- Large doses of parenteral antimicrobials usually are necessary to achieve bactericidal concentrations within vegetations.
- An extended duration of therapy is required, even for susceptible pathogens, because microorganisms are enclosed within valvular vegetations and fibrin deposits.
- Treatment of IE should be started promptly. Three sets of blood cultures should be drawn at 30-min intervals before initiation of antibiotics. The initial choice of empirical treatment depends on several considerations:
  1. Whether the patient has received previous antibiotic therapy
  2. Whether the infection affects a native valve or a prosthesis [and if so, when surgery was performed (early vs. late PVE)]
  3. The place of the infection (community, nosocomial, or nonnosocomial healthcare-associated IE) and knowledge of the local epidemiology, especially for antibiotic resistance and specific genuine culture-negative pathogens
  4. Cloxacillin/cefazolin administration is associated with lower mortality rates than other beta-lactams, including amoxicillin/clavulanic acid or ampicillin/sulbactam, and vancomycin for empirically treating MSSA endocarditis.
# Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Class</th>
<th>Level</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community-acquired native valves or late prosthetic valves (≥ 12 months post surgery) endocarditis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin with (Flu)cloxacin or oxacillin with Gentamicin</td>
<td>12 g/day i.v. in 4–6 doses</td>
<td>IIa</td>
<td>C</td>
<td>Patients with BCNIE should be treated in consultation with an ID specialist.</td>
</tr>
<tr>
<td></td>
<td>12 g/day i.v. in 4–6 doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin with Gentamicin</td>
<td>30–60 mg/kg/day i.v. in 2–3 doses</td>
<td>IIb</td>
<td>C</td>
<td>For penicillin-allergic patients</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Early PVE (&lt;12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin with Gentamicin</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>IIb</td>
<td>C</td>
<td>Rifampin is only recommended for PVE and it should be started 3–5 days later than vancomycin and gentamicin has been suggested by some experts. In healthcare associated native valve endocarditis, some experts recommend in settings with a prevalence of MRSA infections &gt;5% the combination of cloxacillin plus vancomycin until they have the final S. aureus identification</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BCNIE = blood culture-negative infective endocarditis; ID = infectious disease; i.m. = intramuscular; i.v. = intravenous; PVE = prostatic valve endocarditis.
STREPTOCOCCAL ENDOCARDITIS

- Most viridans streptococci are exquisitely sensitive to penicillin G with minimal inhibitory concentrations (MICs) less than or equal to 0.12 mcg/mL.
- The MIC should be determined for all viridans streptococci and the results used to guide therapy.
- Approximately 10% to 20% are moderately susceptible (MIC 0.12 to 0.5 mcg/mL).

### Antibiotic treatment of infective endocarditis due to oral streptococci and Streptococcus bovis group

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strains penicillin-susceptible (MIC ≤ 0.125 mg/L)</strong> oral and digestive streptococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard treatment: 4-week duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>12–18 million U/day iv. either in 4–6 doses or continuously</td>
<td>4</td>
<td>I</td>
<td>B</td>
<td>68</td>
<td>Preferred in patients &gt; 65 years or with impaired renal or V11 (vestibulocochlear) cranial nerve functions. 4-week therapy recommended for patients with PVE.</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>100–200 mg/kg/day iv. in 4–6 doses</td>
<td>4</td>
<td>I</td>
<td>B</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Ceftiraxone</td>
<td>2 g/day iv. or im. in 1 dose</td>
<td>1</td>
<td>I</td>
<td>B</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td><strong>Paediatric doses</strong></td>
<td>Penicillin G 200,000 U/kg/day iv. in 4–6 divided doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>300 mg/kg/day iv. in 4–6 equally divided doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftiraxone</td>
<td>100 mg/kg/day iv. or im. in 1 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Standard treatment: 2-week duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>12–18 million U/day iv. either in 4–6 doses or continuously</td>
<td>2</td>
<td>I</td>
<td>B</td>
<td>68, 127, 135–138</td>
<td>Only recommended in patients with non-complicated NVE with normal renal function.</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>100–200 mg/kg/day iv. in 4–6 doses</td>
<td>2</td>
<td>I</td>
<td>B</td>
<td>135–138</td>
<td></td>
</tr>
<tr>
<td>Ceftiraxone</td>
<td>2 g/day iv. or im. in 1 dose</td>
<td>2</td>
<td>I</td>
<td>B</td>
<td>135–138</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3 mg/kg/day iv. or im. in 1 dose</td>
<td>2</td>
<td>I</td>
<td>B</td>
<td>135–138</td>
<td></td>
</tr>
<tr>
<td>Netilmicin</td>
<td>4–5 mg/kg/day iv. in 1 dose</td>
<td>2</td>
<td>I</td>
<td>B</td>
<td>135–138</td>
<td>Netilmicin is not available in all European countries.</td>
</tr>
</tbody>
</table>

**Paediatric doses:**

- Penicillin G, amoxicillin, and ceftiraxone as above.
- Gentamicin: 3 mg/kg/day iv. or im. in 1 dose or 3 equally divided doses.

*European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis.*
S. aureus has become more prevalent as a cause of endocarditis because of increased IV drug abuse, frequent use of peripheral and central venous catheters, and valve-replacement surgery.

Coagulase-negative staphylococci (CNST, usually S. epidermidis) are prominent causes of Prosthetic valve endocarditis (PVE). The recommended therapy for patients with left-sided IE caused by methicillin-sensitive S. aureus (MSSA) is 4 to 6 weeks of nafcillin or oxacillin, often combined with a short course of gentamicin.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration (weeks)</th>
<th>Class&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;h&lt;/sup&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native valves</td>
<td>Methicillin-susceptible staphylococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Flucloxacillin or oxacillin)</td>
<td>12 g/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td>I</td>
<td>B</td>
<td>6,8, 128, 135, 136, 158</td>
<td>Gentamicin addition is not recommended because clinical benefit has not been demonstrated and there is increased renal toxicity</td>
</tr>
<tr>
<td></td>
<td>Paediatric doses:&lt;sup&gt;a&lt;/sup&gt;</td>
<td>200–300 mg/kg/day i.v. in 4–6 equally divided doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative therapy*</td>
<td>Cotrimoxazole&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Sulphamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)</td>
<td>1 i.v. + 5 oral intake</td>
<td>IIb</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>with</td>
<td>Clindamycin</td>
<td>1800 mg/day i.v. in 3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paediatric doses:&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sulphamethoxazole 60 mg/kg/day and Trimethoprim 12 mg/kg/day (i.v. in 2 doses) Clindamycin 40 mg/kg/day (i.v. in 3 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Penicillin-allergic patients<sup>b</sup> or methicillin-resistant staphylococci

| | | | | | | |
| Vancomycin<sup>**</sup> | 30–60 mg/kg/day i.v. in 2–3 doses | 4–6 | I | B | 6,8, 128, 135, 136 | Cefalosporins (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis |
| | Paediatric doses:<sup>a</sup> | 40 mg/kg/day i.v. in 2–3 equally divided doses | | | | |
| Alternative therapy**: | Daptomycin<sup>**</sup> | 10 mg/kg/day i.v. once daily | 4–6 | Ila | C | Daptomycin is superior to vancomycin for MSSA and MRSA bacteremia with vancomycin MIC > 1 mg/L. |
| | Paediatric doses:<sup>a</sup> | 10 mg/kg/day i.v. once daily | | | | |
TREATMENT OF STAPHYLOCOCCUS ENDocarditis IN IV DRUG ABUSERS

- Treatment of Staphylococcus Endocarditis in IV Drug Abusers IE in IV drug abusers is most frequently (60% to 70%) caused by S. aureus, although other organisms may be more common in certain geographic locations.

- **Standard treatment for MSSA consists of 4 weeks of therapy with a penicillinase-resistant penicillin.**

- A 2-week course of nafcillin or oxacillin plus an aminoglycoside may be effective.

- Short-course vancomycin, in place of nafcillin or oxacillin, appears to be ineffective.
• **Enterococci cause 5% to 18% of endocarditis cases and are noteworthy for the following reasons:**

  (1) no single antibiotic is bactericidal

  (2) MICs to penicillin are relatively high (1 to 25 mcg/mL)

  (3) they are intrinsically resistant to all cephalosporins and relatively resistant to aminoglycosides (i.e., “low-level” aminoglycoside resistance)

  (4) combinations of a cell wall–active agent, such as a penicillin or vancomycin, plus an aminoglycoside are necessary for killing

  (5) resistance to all available drugs is increasing
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage and route</th>
<th>Duration, weeks</th>
<th>Class</th>
<th>Level</th>
<th>Ref.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-lactam and gentamicin-susceptible strains (for resistant isolates see a,b,c)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin*</td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>4–6</td>
<td>I</td>
<td>B</td>
<td>6,8, 129, 135, 136, 186</td>
<td>6-week therapy recommended for patients with &gt;3 months symptoms or PVE</td>
</tr>
<tr>
<td>with Gentamicin*</td>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td>2–6**</td>
<td>I</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paediatric doses:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin with Ceftiraxone</td>
<td>200 mg/kg/day i.v. in 4–6 doses</td>
<td>6</td>
<td>I</td>
<td>B</td>
<td>183–185</td>
<td>This combination is active against <em>Enterococcus faecalis</em> strains with and without HLAR, being the combination of choice in patients with HLAR <em>E. faecalis</em> endocarditis.</td>
</tr>
<tr>
<td></td>
<td>4 g/day i.v. or i.m. in 2 doses</td>
<td>6</td>
<td>I</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Paediatric doses:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin* with Gentamicin*</td>
<td>30 mg/kg/day i.v. in 2 doses</td>
<td>6</td>
<td>I</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/day i.v. or i.m. in 1 dose</td>
<td>6</td>
<td>I</td>
<td>C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HLAR**: high-level aminoglycoside resistance; **IE**: infective endocarditis; **MIC**: minimum inhibitory concentration; **PBP**: penicillin binding protein; **PVE**: prosthetic valve endocarditis.

*High-level resistance to gentamicin (MIC > 500 mg/L): if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses.

**Beta-lactam resistance:** (i) if due to beta-lactamase production, replace amoxicillin with amoxicillin–sulbactam or amoxicillin with amoxicillin–clavulanate; (ii) if due to PBP5

European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis
RIGHT-SIDED INFECTIVE ENDOCARDITIS TREATMENT

• Vegetation length > 20 mm and fungal aetiology were the main predictors of death
• The choice of empiric antimicrobial therapy depends on the suspected microorganism, type of drug and solvent used by the addict and the infection location
• In any case, S. aureus must always be covered
• Initial treatment includes penicillinase-resistant penicillins, vancomycin or daptomycin, depending on the local prevalence of MRSA, in combination with gentamicin
• If the patient is a pentazocine addict, an antipseudomonas agent should be added

• Because of limited bactericidal activity, poor penetration into vegetations and increased drug clearance in IVDAs, glycopeptides (vancomycin) should not be used in a 2-week treatment
• The standard 4–6-week regimen must be used in the following situations:
  † Slow clinical or microbiological response (> 96 h) to antibiotic therapy
  † Right-sided IE complicated by right HF, vegetations >20 mm, acute respiratory failure, septic metastatic foci outside the lungs (including empyema) or extracardiac complications, e.g. acute renal failure
  † Therapy with antibiotics other than penicillinase-resistant penicillins
  † IVDA with severe immunosuppression (CD4 count <200 cells/mL) with or without AIDS or
  † Associated left-sided IE

European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis
## List of medications prescribed for patient in hospital:

<table>
<thead>
<tr>
<th>Antibacterial treatment</th>
<th>Other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Levofloxacin 500mg IV 1 time/day from 05/09 till 15/09/15</td>
<td>• Dexamethasone 8mg IV in 200ml of 5% dextrose solution #3 (low BP was)</td>
</tr>
<tr>
<td>• Amoxicillin/clavulonic acid IV 1000mg 2 times/day from 05/09 till 13/10/15</td>
<td>• Trifas (torasemid) 20 mg IV 1 time/day then 10 mg/day orally</td>
</tr>
<tr>
<td>• Vancomycin 1gr IV 2 times/day from 14/09 till 30/09/15 (patient cannot continue therapy due to financial problems)</td>
<td>• Ampril (ramipril - eACE) 2.5 mg / day</td>
</tr>
<tr>
<td>• Gentamycin 80mg 2 times/day IM from 19/09 till 13/10/15</td>
<td>• Bisoprolol (b-blocker) 5 mg 1 time/day</td>
</tr>
<tr>
<td>• “Biseptol” 480 mg 2 tabl 3 times/day from 22/09 till 13/10/15</td>
<td>• “Glutargin” (hepatoprotector) 1 tabl 3 times/day from 14/09 till 13/10/15</td>
</tr>
<tr>
<td>• Levomicetin (Chloramphenicol) 1gr 4 times/day IV from 02/10 till 13/10/15</td>
<td>• Vicasol 1.0 ml IM 5 days</td>
</tr>
<tr>
<td></td>
<td>• Aminocapronic acid 100 ml IV #1</td>
</tr>
<tr>
<td></td>
<td>• Blood transfusion (erythrocytes mass) 333ml gr IV (RH+) IV 24/09/15</td>
</tr>
</tbody>
</table>
COMPLICATIONS

Four etiologies:

- Embolic
- Local spread of infection
- Metastatic spread of infection
- Formation of immune complexes – glomerulonephritis and arthritis
EMBOLIC COMPLICATIONS

- Occur in up to 40% of patients with IE
- Predictors of embolization
- Size of vegetation
- Left-sided vegetations
- Fungal pathogens, S. aureus, and Strep. Bovis
- Incidence decreases significantly after initiation of effective antibiotics

THEY INCLUDE:

- Stroke
- Myocardial Infarction
- Fragments of valvular vegetation
- Vegetation-induced stenosis of coronary ostia
- Ischemic limbs
- Hypoxia from pulmonary emboli
- Abdominal pain (splenic or renal infarction)
LOCAL SPREAD OF INFECTION

- Heart failure
- **Extensive valvular damage**
- Paravalvular abscess (30-40%)
- **Most common in aortic valve, IVDA, and S. aureus**
- May extend into adjacent conduction tissue causing arrhythmias
- Higher rates of embolization and mortality
- **Pericarditis Fistulous intracardiac connections**

![](image)
METASTATIC SPREAD OF INFECTION

- Metastatic abscess
- Kidneys, spleen, brain, soft tissues
- Meningitis and/or encephalitis
- Vertebral osteomyelitis
- Septic arthritis
# Poor Prognostic Factors

## Patient characteristics
- Older age
- Prosthetic valve IE
- Diabetes mellitus
- Comorbidity (e.g., frailty, immunosuppression, renal or pulmonary disease)

## Clinical complications of IE
- Heart failure
- Renal failure
- >Moderate area of ischaemic stroke
- Brain haemorrhage
- Septic shock

## Microorganism
- *Staphylococcus aureus*
- Fungi
- Non-HACEK Gram-negative bacilli

## Echocardiographic findings
- Periannular complications
- Severe left-sided valve regurgitation
- Low left ventricular ejection fraction
- Pulmonary hypertension
- Large vegetations
- Severe prosthetic valve dysfunction
- Premature mitral valve closure and other signs of elevated diastolic pressures

[http://eurheartj.oxfordjournals.org/content/early/2015/08/28/eurheartj.ehv319]
EVALUATION OF THERAPEUTIC OUTCOMES

assessment of signs and symptoms, blood cultures, microbiologic tests (e.g., MIC, minimum bactericidal concentration [MBC], or serum bactericidal titers), serum drug concentrations, and other tests to evaluate organ function.

• Persistence of fever beyond 1 week may indicate ineffective antimicrobial therapy, emboli, infections of intravascular catheters, or drug reactions
• In some patients, low-grade fever may persist even with appropriate antimicrobial therapy
• After the initiation of therapy, blood cultures should be rechecked until they are negative
DOES THIS PATIENT REQUIRE CARDIAC SURGICAL INTERVENTION?

**Surgery Required for Optimal Outcome**
- Moderate to severe congestive heart failure due to valve dysfunction
- Partially dehisced unstable prosthetic valve
- Persistent bacteremia despite optimal antimicrobial therapy
- Lack of effective microbicidal therapy (e.g. fungal or brucella endocarditis), S. aures, prosthetic valve endocarditis with an intracardiac complication
- Relapse of prosthetic valve endocarditis after optimal antimicrobial therapy

**Surgery to Be Strongly Considered for Improved Outcomes**
- Perivalvular extension of infection
- Poorly responsive S. aures endocarditis involving the aortic or mitral valve
- Large (>10 mm in diameter) hypermobile vegetations with increased risk of embolism, particularly with prior embolic event or with significant valve dysfunction
- Persistent unexplained fever (more than 10 days) in culture-negative native valve endocarditis
- Poorly responsive or relapsed endocarditis due to highly antibiotic-resistant enterococci or Gram-negative bacilli

---

**Indications for surgical treatment of right-sided infective endocarditis**

- **Microorganisms difficult to eradicate (e.g. persistent fungi) or bacteremia for > 7 days (e.g. S. aures, P. aeruginosa) despite adequate antimicrobial therapy or Persistent tricuspid valve vegetations > 20 mm after recurrent pulmonary embolism with or without concomitant right heart failure or Right HF secondary to severe tricuspid regurgitation with poor response to diuretic therapy**

---

European Society of Cardiology 2015 algorithm for diagnosis of infective endocarditis
Antimicrobial prophylaxis is used to prevent IE in patients believed to be at high risk.

- The use of antimicrobials for this purpose requires consideration of the types of patients who are at risk; the procedures causing bacteremia; the organisms that are likely to cause endocarditis; and the pharmacokinetics, spectrum, cost, and ease of administration of available agents.

- Antibiotic prophylaxis should only be considered for patients at highest risk for endocarditis, undergoing at risk dental procedures. The main targets for antibiotic prophylaxis in these patients are oral streptococci.

- In the case of an established infection or if antibiotic therapy is indicated to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary tract procedure.

- Case reports of IE after piercing and tattooing are increasing, particularly when piercing involves the tongue, patients should be informed about the hazards of piercing and tattooing and these procedures should be discouraged not only in high-risk patients, but also in those with native valve disease.

- The most frequent microorganisms underlying early (1 year after surgery) prosthetic valve infections are coagulase-negative staphylococci (CoNS) and Staphylococcus aureus. Prophylaxis should be started immediately before the procedure, repeated if the procedure is prolonged and terminated 48h afterwards.
THANK YOU!

MANISH KUMAR
GROUP: 527
COURSE: 5