INFECTIVE ENDOCARDITIS (IE)

DEFINITION OF ENDOCARDITIS

Infective endocarditis is the inflammation of the endocardium or of the endocardial surface at the level of the septal defect, on chordae tendinae or in the mural endocardium; in general terms, is defined as the infection of heart valves in the vast majority of cases.
There are different classifications according to the clinical presentation (acute/hyper-acute or subacute-chronic), according to the organism, etiology and progression, infection of a native valve or prosthetic valve.

The concept of endocarditis as a disease is mainly due to Sir William Osler, a medical doctor, who, in 1885, presented a sort of unifying theory in which he said that only susceptible patients could develop endocarditis which is a relatively rare disease. These patients could develop a mycotic endocarditis due to mycotic growths on their valves followed by transference to distant parts of microorganisms leading to the formation of an embolus which is the most important complication of endocarditis.

The characteristic lesion is the vegetation which is a sort of matrix made by fibrin, components of blood, microorganisms and inflammatory cells that can grow on the valve or on the endocardium. Normal valvular endothelium is resistant to bacterial colonization; indeed, we are subjected to a lot of bacteria in our lives (even asymptomatic) and thanks to this resistance in order to develop endocarditis the simultaneous occurrence of several independent factors is needed. These factors are:

- Alteration of the cardiac valve surface to produce a suitable site of attachment for bacteria permitting their colonization. This is the case of the areas of turbulence or other alterations of the valvular surface.
- Presence of bacteria in the blood (bacteremia) that are able to attach and proliferate on the valvular surface.
- Creation of a vegetation by burying of proliferating organisms within a protective matrix of serum molecules (such as fibrin) and platelets.

PATHOGENESIS

- **Altered valve surface**: there are some animal experiments that suggests that endocarditis is almost impossible to establish on a perfect valve surface.
  The first step of endocarditis is the deposition on the surface of fibrin and platelets giving rise to a **nonbacterial thrombotic vegetation (NBTC)**. Bacteria find this very suitable environment and attach to it and then are covered by more fibrin and protected from neutrophils. Bacteria start to divide permitting the formation of a mature vegetation.
- **Hemodynamic factors**: the presence of hemodynamic alterations and turbulence of blood in correspondence of valves can help the bacterial colonization. The degrees of turbulence of valvular stenosis, for example, can make longer the possible time of attachment of bacteria to the surface.

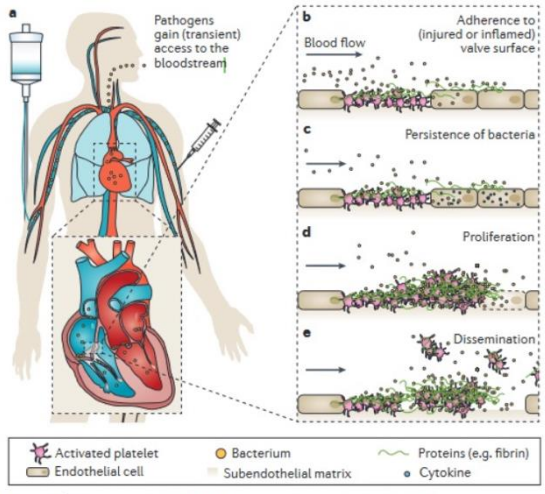


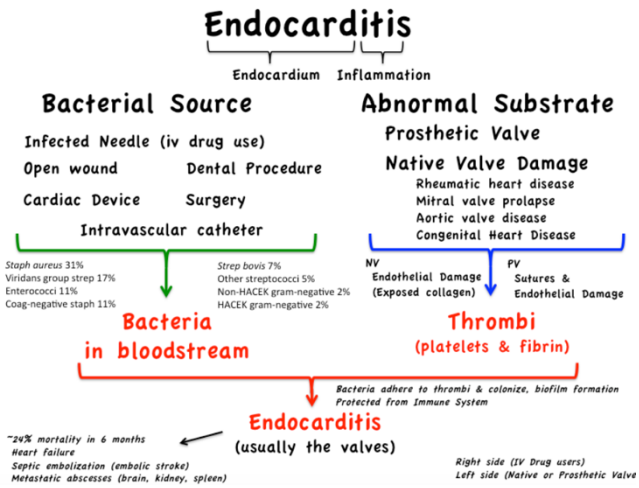
Figure 2 | **Pathogenesis of IE. a** | Pathogens gain access to the bloodstream, for example, via an intravenous catheter, injection drug use or from a dental source. **b** | Pathogens adhere to an area of abnormal cardiac valve surface. **c** | Some pathogens, such as *Staphylococcus aureus*, obtain intracellular access to the valve endothelium. **d** | The infected vegetation is created by burying of the proliferating organism within a protective matrix of serum molecules. **e** | Vegetation particles can detach and disseminate to form emboli. These may lead to complications, such as ischaemic stroke, mycotic aneurysms and infarcts or abscesses at remote sites. IE, infective endocarditis. Figure from REF. 204, Nature Publishing Group.

In *fig.1* is possible to see that bacteria can enter the bloodstream by an intravenous catheter in hospital or by injection of drugs and attach in case of alteration of part of the endothelium due to lesions or

inflammations due to rheumatic disorders, atherosclerosis, turbulence or any kind of valvulopathy. They start proliferating and then they disseminate creating emboli.

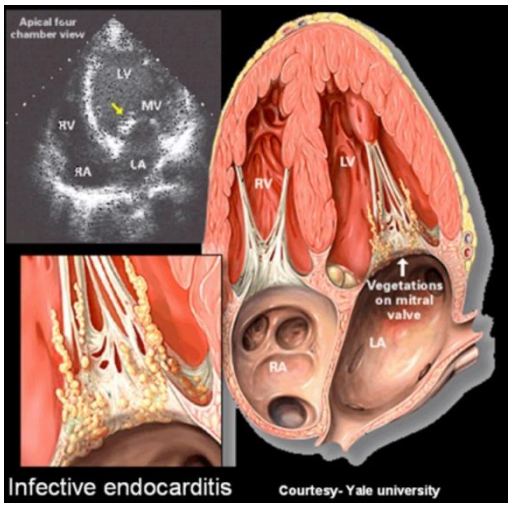
SITE OF INFECTION

Left valves are more commonly infected than right ones and the aortic valve is more commonly infected then the mitral one. In some cases, there could be the concomitant infection of mitral and aortic valve. The aortic infection is the most frequent and the vegetation is usually on the ventricular side affecting all the three cusps. The problem is that in case of aggressive bacteria such as Staphylococcus Aureus you can have damage of the valve with perforation and consequent dysfunction or even root abscesses. In case of mitral involvement, the problem is related to dysfunction by rupture of chordae tendinae.



In *fig. 2* we have a schematic view of the pathogenesis of endocarditis. On the left we can see the important factors for the bacterial source. The most important agents are Staphylococci and Streptococci. On the right is indicated how bacteria attach to an abnormal substrate leading to the formation of thrombi. Prosthetic valve per se, for example, is considered a surface suitable for bacterial attachment.

In *fig. 3* the mitral valve is represented; some vegetations (yellow nodules) are present on the ventricular side. They can damage the chordae tendinae. In the upper part of *fig. 3* there is an echocardiography in which it is possible to see the mass of vegetation *(yellow arrow)*.



EPIDEMIOLOGY

From the epidemiological point of view the scenario has changed in the last decades due to the increased longevity of people and also due to new predisposing factors such as the widespread use of prosthetic valves and also due to the potential of nosocomial infections.
In US and Western countries endocarditis is considered, from a cardiological point of view, quite a rare disease, between 2 and 6 cases per 100 000 person/year. More frequent in males than in females with a mean age of 47-69, while in the past was more frequent in young adults between 30-40 years old and this change is due to the change in predisposing factors; in the past, the most important predisposing factor were rheumatic diseases that affected mostly young people, now these diseases are very infrequent in Western countries, while now the most important factor is the alteration of the valvular function due to the increased longevity and increased exposure to nosocomial bacteria. Group of people that remain at very high risk are the intravenous drug users (2000 person/year).

PROSTHETIC VALVES

The use of prosthetic valves represents 7-25% of cases of infective endocarditis. The rate of risk is higher in the first month after surgery and is higher for mechanical valves than biological ones.

- **Early** endocarditis: within 2 months surgery
- **Late** endocarditis: 12 months post surgery

In the middle there is a sort of grey zone with a gradient of distribution form early to late. The type of onset (early or late) is due to a different kind of etiology. The early one is hospital acquired, related to surgery, the late one is a community acquired endocarditis and is similar to the endocarditis of native valves.

NOSOCOMIAL INFECTIVE ENDOCARDITIS

In 7-29% of cases is due to hospital materials, such as intravascular devices, or due procedure on the genitourinary and gastrointestinal tract.

RISK FACTORS

There are cardiac and non-cardiac risk factors:

- Cardiac risk factors:
    - Previous infective endocarditis: this is one of the most important risk factors due to the alteration of the valvular surface
    - Valvular heart disease
    - Prosthetic heart valve
    - Central venous or arterial catheter
    - Transvenous cardiac implantable electronic device
    - Congenital heart disease

- Non-cardiac risk factors:
    - Central venous catheter
    - People who inject drugs
    - Immunosuppression
    - Recent dental or surgical procedures
    - Recent hospitalization
    - Hemodialysis

We have to keep in mind all these possibilities in order to have an idea of the possible diagnosis for the patient.

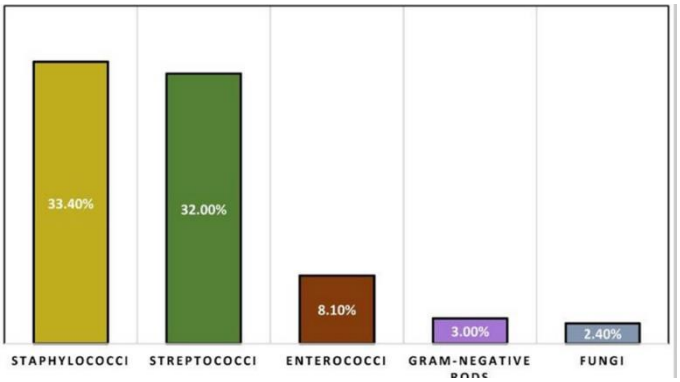
- High risk factors:
    - Previous IE
    - Aortic valve disease
    - Rheumatic valve disease (not so frequent now)
    - Prosthetic valve
    - Congenital heart defects

- Moderate risk:
    - Mitral stenosis
    - Pulmonary stenosis
    - Tricuspid valve defects

- HIV infection:
    - A number of cases of IE have been reported in patients with HIV infection
    - It has been suggested that HIV infection is an independent risk factor for IE in IDU

- Rheumatic valve disease:
    - Predisposition for young in some countries 37%-76% of cases
    - Mitral 85%, Aortic 50%
    - Degenerative valvular lesions
    - MV Prolapse and associated mitral regurgitation - 5 to 8 times higher IE risk
    - Aortic valve disease (stenosis or/and regurgitation) is present in 12 to 30 % of cases

ETIOLOGY



Which are the bacteria mostly involved in this disease? Most of them are Gram + and very common ones are **Streptococci**:

- Viridans streptococci or alpha-hemolytic streptococci are present in the oral microbioma (S. mitis, S. sanguis, S. oralis)
- S. bovis group: the most important is S. gallolyticus. These bacteria are part of the gastrointestinal microbiota and generally the presence of endocarditis caused by them is associated with the presence of a carcinoma in the colon, indeed it is important to perform a colonoscopy. Per se these bacteria are not dangerous.

Another group pf bacteria responsible for the diseases is the one of **Enterococci**, in particular E. faecalis and E. faecium. They are very specific for the valves and are associated with gastrointestinal and genitourinary tract procedures. It is important to remember that approximately 10% of patients with enterococcal bacteremia can develop endocarditis.

Staphylococci are the most important bacteria causing endocarditis, in particular S. aureus that has a high degree of virulence which leads to different clinical courses. Also coagulase-negative staphylococci can cause endocarditis, they tend to localize on prosthetic valves.

There are few cases due to Gram – rods:

- HACEK group (*Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*) that are part of the oral microbioma with very slow and that need extended culture (7-10 days) to be isolated growth.
- E. coli, Klebisiella
- Pseudomonas aeruginosa
- Nisseria gonorrhoae

Other etiological agents:

- Fungi, such as Candida species which generates a very severe clinical condition especially in hospitalized patients and immunosuppressed patients.
- Q fever
- Chlamydia
- Bartonella
- Legionella

In *fig. 5* we can see the clear difference in the early infection (within 2 months) and late infection (after

1 year) in the case of prosthetic valves. Within 2 months we have a nosocomial infection, the most frequent agents are coagulase – staphylococci and then S. aureus. After 12 months the epidemiology is very similar to the one of endocarditis on native valves; streptococci are the main agents involved, followed by staphylococci and then by coagulase – staphylococci.

TABLE 1. MICROBIOLOGIC FEATURES OF NATIVE-VALVE AND PROSTHETIC-VALVE ENDOCARDITIS.

PATHOGEN	NATIVE-VALVE ENDOCARDITIS				PROSTHETIC-VALVE ENDOCARDITIS		
	NEONATES	2 MO–15 YR OF AGE	16–60 YR OF AGE	>60 YR OF AGE	EARLY (<60 DAYS AFTER PROCEDURE)	INTERMEDIATE (60 DAYS–12 MO AFTER PROCEDURE)	LATE (>12 MO AFTER PROCEDURE)
	approximate percentage of cases						
Streptococcus species	15–20	40–50	45–65	30–45	1	7–10	30–33
Staphylococcus aureus	40–50	22–27	30–40	25–30	20–24	10–15	15–20
Coagulase-negative staphylococci	8–12	4–7	4–8	3–5	30–35	30–35	10–12
Enterococcus species	<1	3–6	5–8	14–17	5–10	10–15	8–12
Gram-negative bacilli	8–12	4–6	4–10	5	10–15	2–4	4–7
Fungi	8–12	1–3	1–3	1–2	5–10	10–15	1
Culture-negative and HACEK organisms*	2–6	0–15	3–10	5	3–7	3–7	3–8
Diphtheroids	<1	<1	<1	<1	5–7	2–5	2–3
Polymicrobial	3–5	<1	1–2	1–3	2–4	4–7	3–7

*Patients whose blood cultures were rendered negative by prior antibiotic treatment are excluded. HACEK denotes haemophilus species (*Haemophilus paninfluenzae, H. aphrophilus,* and *H. parnphrophilus*), *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae.*

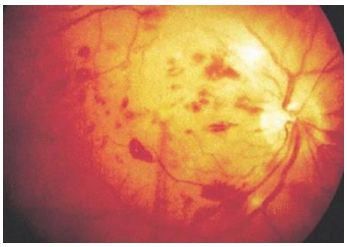
SYMPTOMS

From a clinical point of view, we can have a patient presenting with an acute form or with a subacute form.

- **Acute form**: patient with fever, chills, shortness of breath, chest pain; all these symptoms usually appear after 1-2 weeks from the initiating bacteremia. This form is mainly caused by S. aureus which is a very virulent agent.
- **Subacute form**: lower symptoms such as lower grade fever, weight loss, fatigue, arthralgia and myalgia. This form is mainly caused by S. epidermidis.
  When should I suspect of a subacute infective endocarditis (SBE)? The fever is of unknown origin (FUO), low grade and intermittent (4-10 days). Another sign is the presence of heart murmurs or worsening of preexistent heart murmurs.

  Patients with endocarditis are subjected to embolization. During the physical examination is important to notice the presence of some skin signs which are all due to microembolizations.

  - petechiae (on extremities or mucous membranes such as conjunctiva)
  - subungual hemorrhages (*Fig. 6*, linear lesions under the nail bed)
  - Osler nodes (*Fig. 7*, specific of endocarditis, painful located on the pulp of fingers and toes, more common in subacute IE)
  - Janeway lesions (*Fig. 8*, erythematous, blanching macules, not painful and located on palms and soles)
  - Roth spots (*Fig. 9*, present at the retina level, are areas of embolization which can be seen during the ophthalmological consultation).



In the case of acute bacterial endocarditis (ABE) is easier to find signs of microembolization:

- Stroke: this is the most common neurologic sign
- Renal failure
- Septic emboli
- Sepsis

- Congestive heart failure: due to local damage of the valves

When we see the patient for the first time sometimes complications are already present, especially in case of acute infective endocarditis. So, it is important to evaluate the neurological activity of the patient, the presence of micro emboli etc.

A case of difficult diagnosis is when a prosthetic valve is present; usually bacteria with low virulence are involved, such as coagulase – streptococci. The patient usually has low fever of unknown origin, but in case of early involvement we can have also an acute presentation, a local invasive endocarditis with congestive heart failure and murmurs.

DIAGNOSIS

Diagnosis of IE is based on:

1. Clinical suspicion:
    a. Fever of unknown origin
    b. Evaluation of risk factors
    c. Physical examination

Definitions of the 2023 European Society of Cardiology modified diagnostic criteria of infective endocarditis (1) ESC

Major criteria
(i) Blood cultures positive for IE
(a) Typical microorganisms consistent with IE from two separate blood cultures:
Oral streptococci, *Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group, *S. aureus*, ***E. faecalis***
(b) Microorganisms consistent with IE from continuously positive blood cultures:
• ≥2 positive blood cultures of blood samples drawn >12 h apart
• All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart)
(c) Single positive blood culture for *C. burnetii* or phase I IgG antibody titre >1:800

2. Consistent microbiological data: in 2023 the European Society of Cardiology defined the modified diagnostic criteria of IE. Inside the blood there must be the presence of bacteria blood culture positive for the most important etiological agents of endocarditis (*Fig. 10*).

3. IE-related cardiac lesions by imaging: echocardiography (TTE= trans-esophageal and TOE= trans-thoracic), cardiac CT, PET.
   In *fig. 11* we have the recommendation for the echocardiography.
   In case of inconclusive echocardiography, we can use cardiac CT especially in patients with native valves, or PET especially in patients with prosthetic valves.

	TTE is recommended as the first-line imaging modality in suspected IE.[166,179]
TOE as a second step	TOE is recommended in all patients with clinical suspicion of IE and a negative or non-diagnostic TTE.[166,178,179]
TOE as a first step	TOE is recommended in patients with clinical suspicion of IE, when a prosthetic heart valve or an intracardiac device is present.[166,178,179]
	Repeating TTE and/or TOE within 5–7 days is recommended in cases of initially negative or inconclusive examination when clinical suspicion of IE remains high.[178]
TOE as second step	TOE is recommended in patients with suspected IE, even in cases with positive TTE, except in isolated right-sided native valve IE with good quality TTE examination and unequivocal echocardiographic findings.[165,166,179]
	Performing an echocardiography should be considered in *S. aureus*, *E. faecalis*, and some *Streptococcus* spp. bacteraemia.[19,149,174]

Sometimes, it can happen that we have the evidence of endocarditis with imaging, but negative blood cultures. There are some rare etiological agents, especially intracellular bacteria, which do not result from blood culture, but just from serology or with other techniques. These agents are:

- Brucella spp.
- C. burnetiid
- Bartonella spp.
- Legionella spp.
- Fungi

Imaging and blood culture are considered the two pillars or major criteria, but there are also 5 minor criteria which are the clinical ones such as fever, predisposing conditions, embolic vascular dissemination, immunological phenomena and microbiological evidence (*Fig. 12*).

Minor criteria are the clinical ones

(i) Predisposing conditions (i.e. predisposing heart condition at high or intermediate risk of IE or PWIDs)[a]

(ii) Fever defined as temperature >38°C

(iii) Embolic vascular dissemination (including those asymptomatic detected by imaging only):

- Major systemic and pulmonary emboli/infarcts and abscesses.
- Haematogenous osteoarticular septic complications (i.e. spondylodiscitis).
- Mycotic aneurysms.
- Intracranial ischaemic/haemorrhagic lesions.
- Conjunctival haemorrhages.
- Janeway's lesions.

(IV) Immunological phenomena:

- Glomerulonephritis.
- Osler nodes and Roth spots.
- Rheumatoid factor.

(V) Microbiological evidence:

- Positive blood culture but does not meet a major criterion as noted above.
- Serological evidence of active infection with organism consistent with IE.

IE Classification (at admission and during follow-up)

Definite: definitive diagnosis in these cases

- 2 major criteria.
- 1 major criterion and at least 3 minor criteria.
- 5 minor criteria.

Possible:

- 1 major criterion and 1 or 2 minor criteria.
- 3–4 minor criteria.

Rejected:

- Does not meet criteria for definite or possible at admission with or without a firm alternative diagnosis.

The IE classification states that we have a **definitive** diagnosis of endocarditis if:

- 2 major criteria are present (blood culture + imaging)
- 1 major criteria and at least 3 minor criteria are present
- 5 minor criteria are present

In the other cases we have a possible diagnosis or a rejected one.

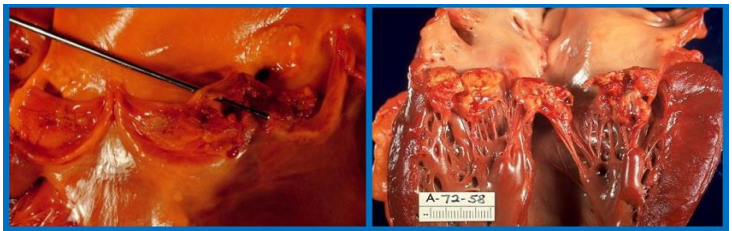
COMPLICATIONS

As we already said, the complications can be present already at the patient presentation. There are four different etiologies:

1. Embolic: the predictors of this complications are the size of the vegetation, the vegetation present on the left side and the presence of S. aureus, S. Bovis and Candida. Embolic complication can lead to stroke, myocardial infarction, ischemic limbs, hypoxia from pulmonary emboli and abdominal pain due to infarction at the level of the kidneys or spleen.

In *fig. 12* we can see a case of right side infective endocarditis; less frequent and specific of intravenous drug users, caused by staphylococci aureus or epidermidis which are present in the normal flora of the skin. The embolization from the right side of the heart goes into the lungs giving rise to pneumonia and pulmonary damages.

2. Local spread of infection can lead to extensive valvular damage, paravalvular abscess (caused mainly by S. aureus, pericarditis (very severe risk of mortality), formation of fistulous intracardiac connections. In *fig. 13* we can see a perforation of the aortic valve and the presence of vegetations over it. On the right of *fig. 13* we have an open mitral valve with acute S. aureus and abscess extending to the myocardium.



Acute *S. aureus* IE with perforation of the aortic valve and aortic valve vegetations.

Acute *S. aureus* IE with mitral valve ring abscess extending into myocardium.

3. Metastatic spread of infection, due to septic emboli which contains organisms inside that can cause a secondary infection in other organs such as kidneys, brain, spleen and soft tissues leading to meningitis, encephalitis, vertebral osteomyelitis and septic arthritis.

4. Formation of immune complexes leading to glomerulonephritis and arthritis.

THERAPY

The principal of therapy is that we have to use drugs in high doses because we have to achieve a sustained bactericidal serum concentration. The duration of the therapy Is about 4-10 weeks because it has to be sufficient to eradicate microorganisms growing in the valvular vegetation. To increase the power of the therapy there are also combinations of antibiotics that can be used together. For this reason, the therapy is usually administered intravenously for the entire duration of the treatment. The right antibiotic must be used at the right dosage and so it is fundamental to know which bacterium is involved in order to understand the MIC (minimum inhibiting concentration) of the antibiotic. It is also important to repeat the blood culture in order to demonstrate that the lesion has been sterilized from bacteria. In general, a first echocardiography is performed before starting the therapy, a second one after 2 weeks to confirm that the antibiotic is working and a last one at the end of the treatment.

- Streptococci/Enterococci therapy
  - Determine MIC of Penicillin (MIC is the value you have on the antibiogram that is needed to define the susceptibility of the microorganism)
  - Penicillin +/- aminoglycoside
  - Ceftriaxone alone
  - Vancomycin +/- aminoglycoside, used in case of allergy or inefficacy of Penicillin
- HACEK group
  - Cefotaxime/ceftriaxone
- Staphylococci
  - If present on native valve
    - Flucloxacillin +/- aminoglycoside
    - Vancomycin +/- aminoglycoside/ rifampicin
  - If present on prosthetic valves (even if i many cases they require surgery, but we can try to maximize the antibiotic treatment with 3 antibiotics at the same time especially with S. aureus)
    - Flucloxacillin + aminoglycoside + rifampicin
    - Vancomycin + aminoglycoside + rifampicin

Until now, the treatment had to be intravenously administered, not orally, but in new guidelines is reported that in some cases, based on the fact that there are no complications, no S. aureus presence etc, we can try with an oral administration of the therapy after 2 weeks of IV treatment (*Fig. 14*). OPAT is the oral therapy

done at home.

SURGICAL THERAPY

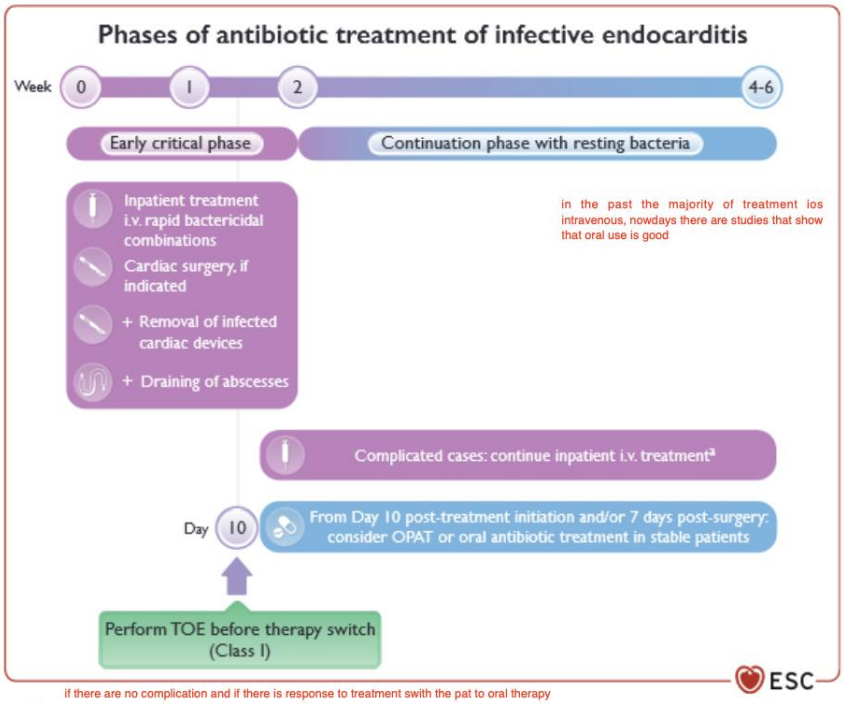


Figure 8 Phases of antibiotic treatment for infective endocarditis in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment. i.v., intravenous; OPAT, outpatient parenteral antibiotic treatment; TOE, transoesophageal echocardiography. [a]Criteria for switching to OPAT or partial oral treatment of endocarditis are given in the Supplementary data online, Table S8.

In some cases, there is a strict indication for surgery, especially if there is:

- local damage such as in congestive heart failure
- perivalvular invasive disease
- uncontrolled infection despite maximal antibiotic therapy (especially with less frequent bacteria, Gram -, which are *Pseudomonas aeruginosa*, *Brucella* species*, Coxiella burnetti, Candida* and fungi)
- presence of prosthetic valve endocarditis
- large vegetations
- major embolus
- heart block.

In *fig. 15*, there is a summary of what we have said about therapy.

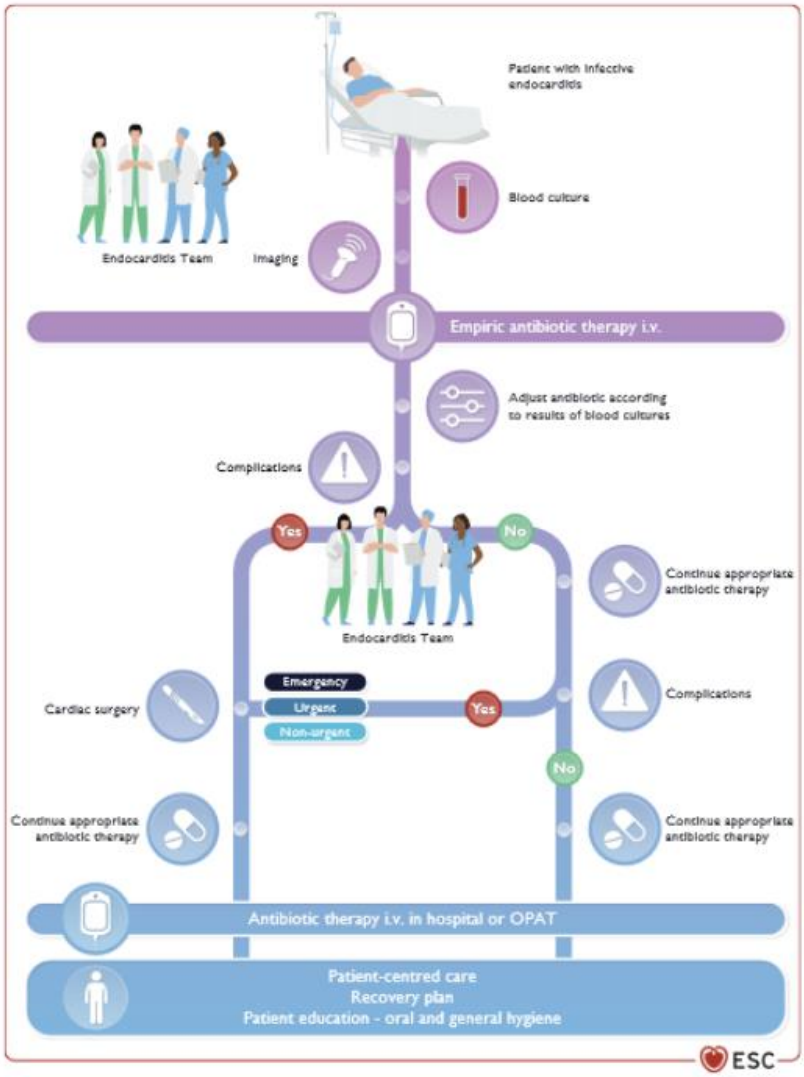


Figure 1 Management of patients with infective endocarditis. i.v., intravenous; OPAT, outpatient parenteral antibiotic therapy.

MORTALITY

The risk of mortality in case of endocarditis is present and depends on several factors:

- organism
- presence of complications
- preexisting conditions
- development of perivalvular or myocardial abscesses
- use of combined antimicrobial and surgical therapy

Mortality related to the infesting agent:

- *Viridans Streptococci* and *S. bovis*: 4-16%
- *Enterococci*:15-25%
- *S. aureus*: 25-47%
- *Q fever*: 5-37% (17% in Ireland)
- *P. aeruginosa,* fungi, *Enterobacteriaceae* > 50%
- Overall mortality 20-25% and for right-sided endocarditis in IVDA (intravenous drug users) is 10%

PROPHYLAXIS

Important thing in terms of prevention especially for those patients that present predisposing conditions such as:

- High or moderate cardiac risk conditions
- Patients that have to undergo dental procedures, rigid bronchoscopy, esophageal procedures, GI mucosal procedures, cystoscopy, prostate surgery.

All these factors can create a high risk for bacteremia and so it is important to do the prophylaxis 1-2 hours before the beginning of the procedure using 2gm of Amoxicillin orally or other drugs.
This prophylaxis decreases the possibility for bacteria to attach on altered valves.

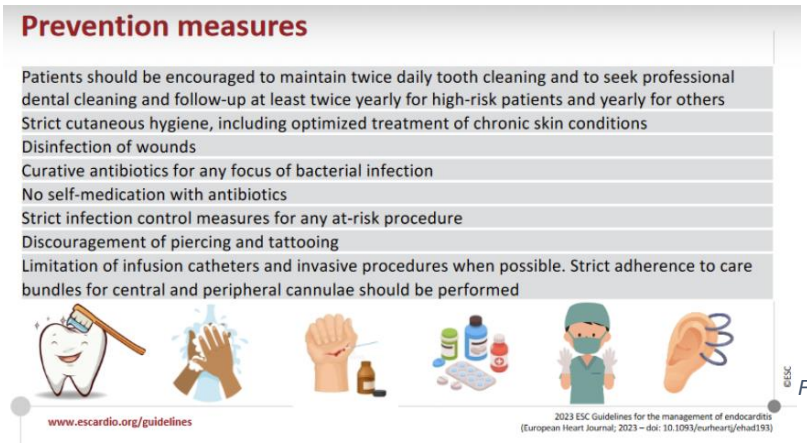


Figure 16

Look at *fig. 16* for prevention measures.