

Consensus Statement on Infective Endocarditis / Abridged Version

Argentine Society of Cardiology

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Abbreviations

ATB	Antibiotic	SBT	Serum bactericidal test
ATM	Antimicrobial	CRP	C-reactive protein
AV	Atrioventricular	SIT	Serum inhibitory test
MIC	Minimum inhibitory concentration	MRI	Magnetic resonance imaging
ECG	Electrocardiogram	MRSA	Methicillin-resistant Staphylococcus aureus
IE	Infective endocarditis	MSSA	Methicillin-sensitive Staphylococcus aureus
TEE	Transesophageal echocardiogram.	CNS	Central nervous system
TTE	Transthoracic echocardiography	CT	Computed tomography
IV	Intravenous	HIV	Human immunodeficiency virus
NYHA	New York Heart Association		

INTRODUCTION

Infective endocarditis (IE) is still an important clinical challenge. Despite progress in diagnostic imaging techniques, the diagnosis of IE is still mostly based on medical criterion, especially on clinical suspicion. The Area of Regulations and Consensuses of the Argentine Society of Cardiology asked an expert panel to update the Consensus Statement on Infective Endocarditis. The spirit of the resulting document is to show the updated scenario of IE, with recommendations aimed at optimizing the diagnosis and treatment, expecting to generate a useful tool for our colleagues in dealing with this complex condition. In particular, the experience obtained in our country over the past 20 years with the Endocarditis Infecciosa en la República Argentina studies (EIRA 1 and 2) was taken into account, together with the relevant scientific information and the recommendations provided by other societies. The final complete version with the corresponding references is available in the website of the Argentine Society of Cardiology. (AGREGAR LINK)

The strength of the recommendation and the level of evidence for the final recommendations were based on the regulations of the Area of Regulations and Consensuses of the SAC:

- **Class I:** Conditions for which there is evidence or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- **Class II:** Conflicting evidence or a divergence of opinion about the usefulness/efficacy of a method, procedure or treatment.
- **Class IIa:** The weight of evidence/opinion is in favor of usefulness/efficacy.
- **Class IIb:** The usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** Conditions for which there is evidence or general agreement that a procedure or treatment is not useful/effective, and in some cases may be harmful.

Levels of evidence:

- **Level of evidence A:** Consistent evidence from well designed, randomized clinical trials or cohort studies to reach statistically sound and biologically significant conclusions.
- **Level of evidence B:** Data derived from a single randomized trial or large non-randomized studies.
- **Level of evidence C:** Data derived from consensus of expert opinions.

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1. COMMITTEE ON DIAGNOSIS AND EVALUATION

INITIAL EVALUATION OF SUSPECTED INFECTIVE ENDOCARDITIS

Class I, Level of evidence C

1. Anamnesis and physical examination. Duke criteria.
2. Laboratory tests: complete blood count, erythrocyte sedimentation rate, BUN and creatinine levels, urinalysis and HIV screening tests.
3. Blood cultures.
4. Initial ECG.
5. Chest X-ray
6. Transthoracic Doppler echocardiography.
7. CT scan or MRI in the presence of neurological signs and symptoms.
8. Contrast-enhanced CT scan, MRI and/or angiography if a cerebral mycotic aneurysm is suspected.
9. CT scan or MRI if a splenic infarction or abscess is suspected.
10. Lumbar puncture if meningitis is suspected.

Class IIa, Level of evidence C

1. Laboratory tests: rheumatoid factor, CRP, other tests.
2. Serial ECG with PR interval measurement.
3. Asymptomatic cerebral mycotic aneurysms: serial angiographies.
4. Central nervous system imaging techniques to rule out mycotic aneurysms in case valve surgery or anticoagulation therapy is required.

Class III, Level of evidence C

1. Central nervous system imaging techniques in the absence of neurological signs and symptoms.

BLOOD CULTURES

Recommendations for blood culture indication, collection and processing in patients with suspected infective endocarditis (Class I, level of evidence B)

Blood cultures are the most important laboratory tests for the diagnosis of IE, and provide information about the etiology and adequate antimicrobial treatment.

1. Blood culture samples must always be collected before initiating antimicrobial therapy.
2. Take three samples. Arterial samples have no advantage over venous samples. In case automated blood culture systems are used, an anaerobic bottle should be added.
3. For an adult, the recommended sample volume should be at least 10 ml of blood (30 ml for the set of blood samples).
4. The blood volume/broth volume ratio should be respected. For conventional blood culture bottles, the optimal ratio is 1:5 to 1:10.
5. The interval between sample draws will depend on the severity of the condition and the need to initiate urgent antimicrobial therapy. In case the blood cultures are negative at 24 hours, three additional samples can be obtained. In patients who received antibiotics within 2 weeks before admission and with stable clinical condition, antibiotic therapy can be delayed and 2 or 3 sets of blood cultures can be obtained every 2 or 3 days. If possible, use commercially available bottles with antibiotic-inactivating resins.
6. An incubation time of 7 days is recommended for conventional systems. For automated blood culture systems, 5 days of incubation are sufficient to detect most microorganisms.
7. If blood cultures are negative after 48 hours of incubation and IE is suspected, special procedures should be considered (particularly if the patient has not received antibiotics). Continue incubation for 3-4 weeks to detect fastidious bacteria with slow growth. HACEK-related microorganisms grow in automated blood culture systems within the first 5 days. Incubation of automated blood culture systems during 3-4 weeks would allow detecting bacteria which grow very slowly as *Bartonella* and some species of *Brucella*.

INDICATIONS OF TRANSTHORACIC DOPPLER ECHOCARDIOGRAPHY IN INFECTIVE ENDOCARDITIS

Class I

1. Detection of vegetations in patients with high clinical suspicion of infective endocarditis even if blood cultures are negative (*Level of evidence B*).
2. Detection and characterization of valvular lesions, the pathophysiological mechanism, hemodynamic severity and ventricular repercussion in patients with known IE (*Level of evidence B*).
3. Detection and assessment of complications or abnormalities during the evolution of IE (shunts, perforations, abscesses, among others) (*Level of evidence B*).
4. Reassessment of patients with high risk IE (clinical impairment, heart failure, persistent or recurrent fever, virulent organism or hemodynamically significant valve lesion) (*Level of evidence C*).
5. Repeated bacteremia with or without proven cause in the presence of heart valve disease or congenital heart defect (*Level of evidence C*).
6. Baseline postoperative evaluation after repair surgery for endocarditis (*Level of evidence C*).
7. Control at the time of antimicrobial therapy completion to assess residual valve morphology and cardiac function (*Level of evidence C*).

Class IIa

1. Follow-up of uncomplicated IE to detect new asymptomatic complications and supervise the size of the vegetation (*Level of evidence B*).
2. Diagnosis of IE in patients with prosthetic valves with fever without bacteremia or new murmur (*Level of evidence C*).

INDICATIONS OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN INFECTIVE ENDOCARDITIS

Class I

1. Evaluation of the severity of valvular lesions in patients with high clinical suspicion of IE with normal or non-diagnostic TTE (*Level of evidence C*).
2. Diagnosis of IE in patients with heart valve disease and positive blood cultures with negative TTE (*Level of evidence C*).
3. Complicated IE or suspicion of complications (abscess, perforation, fistula, embolism of AV block) to define extension and severity not detected by TTE or to improve the sensitivity and accuracy of a positive TTE, especially for the diagnosis of abscesses and to measure the size of the vegetation (*Level of evidence C*).

4. TEE is recommended as first-line assessment for the diagnosis of prosthetic valve IE and to evaluate its complications (*Level of evidence C*).
5. Preoperative evaluation in patients with IE unless the need for surgery is evident on TTE or unless preoperative TEE will delay surgery in urgent cases (*Level of evidence C*).
6. Intraoperative TEE is recommended in patients undergoing valve surgery for IE (*Level of evidence C*).
7. Repeat TEE/TTE after 7 to 10 days in case of initial negative result is recommended when clinical suspicion of IE is high (*Level of evidence B*).

Class IIa

1. Diagnosis of IE in patients with persistent staphylococcal bacteremia of unknown source or with nosocomial staphylococcal bacteremia (*Level of evidence C*).
2. Repeated bacteremia of unknown cause with normal TTE (*Level of evidence C*).

Class III

1. As routine evaluation in native valve IE with technically adequate TTE (*Level of evidence C*).
2. Febrile syndrome with a known source and normal TTE (*Level of evidence C*).

2. COMMITTEE ON ANTIMICROBIAL THERAPY

GENERAL PRINCIPLES FOR ANTIMICROBIAL TREATMENT OF INFECTIVE ENDOCARDITIS

The primary goal of antibiotic treatment is to eradicate infection by sterilizing vegetations. The unique characteristics of infected vegetations (high bacterial density with low metabolic activity within a fibrin and platelet matrix acting as a barrier against host phagocytes) require prolonged use of high-dose bactericidal ATM (alone or in combination) administered intravenously.

The choice of an appropriate antimicrobial therapy, essential for the successful management of IE, should take into account:

- Form of clinical presentation (acute or subacute).
- The valve involved (right-sided or left sided, native or prosthetic).
- Identification of the microorganism and its microbiological characteristics.
- Characteristics of the host (age, renal function, history of antibiotic hypersensitivity, intravenous drug abuser, among others).
- Efficacy and safety of the antimicrobial treatment chosen.
- Adherence to treatment.
- Treatment cost.

The general principles of IE antimicrobial therapy are:

1. **Hospitalization:** Hospitalization is recommended in all patients with suspicion of IE at least during initial evaluation and treatment. It is extremely important to categorize the patient to:

- Define the need for empiric antibiotic therapy.
- Estimate and identify the microorganism responsible for IE.
- Establish the need for surgery.

2. **Consultation with a cardiac surgeon:** Once the diagnosis of IE has been established, it is crucial and essential for the treating team to decide whether there is need for referring the patient to a center with surgical facilities for the best therapeutic approach. In this sense, consultation with a cardiac surgeon (either at the institution where the patient is hospitalized or early transfer to a center with cardiac surgery facilities) is recommended in the following scenarios:

- Left-sided IE with moderate to severe valve regurgitation.
- Left-sided IE with vegetations ≥ 10 mm.
- Heart failure (even in NYHA class I).
- Hemodynamic instability; requiring vasoactive drugs.
- Complications (e. g., abscess, valve perforation, systemic embolism, etc.).
- IE associated with cardiac devices (e.g., prosthetic valves, pacemakers, etc.).

3. **Treatment initiation:** In critically-ill patients, with criteria for sepsis or suspicion of acute IE, blood culture samples should be drawn within 10-20 minutes and empirical treatment should be initiated to control the progression of the disease. In patients with subacute IE or unspecific clinical condition, and who are clinically stable, it is recommended to await the results of blood cultures to choose the most adequate antimicrobial agent, as these patients do not require urgent treatment and empirical therapy may hinder the final diagnosis. If the patient has received ATM therapy within the past 2 weeks and has a stable clinical condition, treatment can be delayed and serial blood cultures should be taken to increase microbiological yield.

In clinically stable patients with IE and negative blood cultures, empirical treatment can be considered in

the following cases: 1) evidence of systemic embolism, and 2) echocardiographic evidence of ≥ 10 mm and/or mobile vegetations, and/or evidence of perivalvular complications.

Experience and clinical criterion will determine the need for urgent antimicrobial treatment in case of suspected IE. In this sense, it is essential to adequately categorize the patients.

Antimicrobial treatment for IE should never be initiated without having obtained blood cultures. The number of bottles and the milliliters of blood obtained are crucial for the diagnosis of the disease (see Blood cultures in Diagnosis and evaluation).

The following should be considered to choose the appropriate treatment:

- Form of clinical presentation (acute or subacute).
- History of previous invasive procedures or hospitalizations.
- Structure involved (valvular or non-valvular).
- Presence of cardiac devices.
- Right or left-sided IE.
- Need for surgery.

4. Dosage and route of administration: Antimicrobial treatment should be administered via intravenous or intramuscular route. In general, ATM agents should be used with:

- Maximum daily doses.
- Equally divided doses.
- Short intervals of drug dosing: every 4-6 hours for penicillin, ampicillin, cephalothin and cefazolin. The half-life of cephalothin is shorter and it should be administered every 4 hours, while cefazolin can be administered every 8 hours.

Other dose schemes should be evaluated (extended infusion, continuous infusion or initial loading dose), especially in critically-ill patients, as these strategies (particularly with drugs of the beta lactam group) have demonstrated better clinical efficacy in different scenarios by improving their pharmacodynamic properties.

The intramuscular route may be considered under certain circumstances, (e. g., for outpatient treatment).

The possibility of prescribing oral ATM for treating IE raised little enthusiasm due to potential difficulties in adherence to this type of treatment and to the erratic absorption of some antibiotics, among other reasons. However, as a consequence of the availability of novel agents, several clinical experiences have demonstrated that oral treatment may play a role in the following scenarios:

- Intravenous drug users with uncomplicated right-sided IE by MSSA.
- Obligate intracellular bacteria (*Coxiella burnetti*, *Brucella spp*).
- Prolonged therapy with immunosuppressants in patients not suitable for valve replacement.
- Switch from intravenous to oral antibiotics to complete treatment in adults with IE due to penicillin sensitive *Streptococcus* (see later) and in children with uncomplicated IE due to sensitive microorganisms.

5. ATM pharmacokinetic/pharmacodynamic features: Over the past years, a significant amount of information has emerged about use of ATM according to their pharmacokinetic and pharmacodynamic features. "Sensitivity" to an antibiotic does NOT mean antibacterial effect or clinical efficacy. It is important to evaluate the need for using dose schemes and routes of administration (loading dose, extended infusion, continuous infusion, or intermittent dose) which allow reaching adequate pharmacodynamic parameters. The indication of an antimicrobial agent should be:

- a. APPROPRIATE: according to the sensitivity of the microorganism;
- b. ADEQUATE: using the correct dose and route of administration to ensure that the antibiotic penetrates the tissue infected and reaches the site of action;
- c. OPTIMAL: considering the pharmacokinetic features of the agent and the effect of the clinical condition of the patient (e. g., weight, sepsis, etc.) and the pharmacodynamic aspects of the agents (whether the effect of the ATM depends on time, concentration or area under the curve).

In general, bactericidal antibiotics are recommended (penicillins, cephalosporins, aminoglycosides, glycopeptides, fluoroquinolones, rifampin, daptomycin, fosfomycin). When the use of combination therapy is necessary, the potential risks of the combination should be considered (possibility of antagonistic effects, adverse effects, costs). Combination therapy should only be used when there is solid evidence and the benefits exceed the risks.

6. Duration: The duration of therapy must be sufficient to ensure complete eradication of microorganisms within vegetations and to avoid relapses. Duration is variable according to the microorganism involved, the valve affected (e. g., right-sided IE), the characteristics of the host (e. g., IV drug users), the type of antimicrobial regime used (single drug or combination therapy) and the presence of eventual complications. The minimum duration of treatment is 2 weeks; yet, in most cases a longer duration of 4 to 6 weeks and even >6 weeks is required for IE associated with prosthetic valves.

7. Monitoring of antimicrobial treatment: Periodical monitoring is recommended with lab tests according to the drugs used and the modality of treatment chosen (at hospital or at home). The serum bactericidal test (SBT) and the serum inhibitory test (SIT) have fallen into disuse. Other special determinations should be evaluated, depending on the microorganism involved (e. g., vancomycin MIC in MRSA, vancomycin trough levels or

minimum vancomycin concentration).

8. **Outpatient treatment:** Antimicrobial outpatient treatment is a new modality that has proved to be effective and safe in carefully selected cases.

3. COMMITTEE ON SURGICAL TREATMENT

INTRODUCTION

Most patients with active IE need to be treated with antibiotics (ATBs) and supportive measures. However, surgery should be considered in the presence of complications or ineffective medical treatment. Valve repair or replacement should be considered in patients with cardiac decompensation due to valve lesion, failure of ATB treatment or recurrent embolism. Once IE has been cured with no need for surgery during the active stage, the indication for valve surgery will depend on the severity of the residual lesion. Recently, the American and European guidelines have modified their recommendations. Of interest, and particularly in the European guidelines, timing of surgery is shown together with the class of recommendation and the level of evidence. Therefore, it seems appropriate to revisit our recommendations in the light of the new findings.

SURGERY IN ACTIVE INFECTIVE ENDOCARDITIS

Recommendations

Class I

1. Heart failure unresponsive to medical treatment with severe acute aortic or mitral valve regurgitation or obstruction in a native valve or due to prosthetic valve dysfunction. Timing = Emergency (*Level of evidence B*).
2. Severe aortic or mitral valve regurgitation or obstruction causing symptoms of heart failure or echocardiographic signs of poor hemodynamic tolerance (pulmonary hypertension and/or early mitral valve closure). Timing = Urgent (*Level of evidence B*).
3. Persistent infection with positive blood cultures (fever, leucocytosis and bacteremia) without other documented extracardiac foci despite 7 to 10 days of appropriate antibiotic therapy. Timing = Urgent (*Level of evidence B*).
4. False aneurysm, fistula, growing vegetation or perivalvular abscess (conduction abnormality of recent onset in aortic valve endocarditis, echocardiographic image seen by TEE), particularly due *Staphylococcus spp*, Gram negative germs or in prosthetic valve endocarditis. Timing = Urgent (*Level of evidence B*).
5. Endocarditis caused by fungi or multiresistant organisms. Timing = Urgent/elective (*Level of evidence B*).
6. Recurrent embolism (>1 episode) after adequate antibiotic therapy with visualization of residual vegetations and absence of other embolic sources. Timing = Urgent (*Level of evidence B*).
7. Definite endocarditis in patients with pacemakers or implantable cardioverter defibrillator devices (demonstrated by persistent fever with persistent positive blood cultures or presence of vegetations by TEE) (device extraction). Timing = Urgent (*Level of evidence B*).

Class IIa

1. Early prosthetic valve endocarditis, particularly due to aggressive germs (*Staphylococcus spp*, Gram negative germs). Timing = Urgent (*Level of evidence B*).
2. Severe aortic or mitral valve regurgitation without heart failure. Timing = Elective (*Level of evidence B*).

Class IIb

1. Large (> 15 mm) mobile vegetations, especially those produced by *Staphylococcus* or Gram negative germs. Timing = Urgent (*Level of evidence B*).
2. Splenic abscess: Surgical drainage and/or splenectomy if percutaneous drainage is not possible. Timing = Urgent (*Level of evidence B*).

Class III

1. Adequate response without complications (*Level of evidence B*).

+ **Emergency surgery: surgery performed within 24 hours. Urgent surgery: within a few days. Elective surgery: after 1–2 weeks of antibiotic therapy.**

We should consider that the results commented correspond to centers with experience in surgery for these type of patients; therefore, the physician should analyze the experience of the surgical team, the availability of the different types of prostheses (homografts, mechanical or biological).

cal prostheses), the complexity of postoperative care and the morbidity and mortality rates of the institution where the patient is treated.

4. PROPHYLAXIS COMMITTEE

Over the past years, different scientific societies have introduced modifications in the traditional recommendations about prophylaxis of IE.

The review of the currently available literature analyzed by our work group emphasizes the lack of evidence about the efficacy of antibiotics to prevent IE. However, some highlights should be mentioned:

- The source of eventual bacteremias: dental procedures, but also daily life activities, as eating or chewing, are possible causes of transient bacteremia. Daily life activities are clearly more frequent than dental procedures, and the magnitude of the bacteremia caused is similar, but there are no prophylactic measures against them.
- The growing resistance of *Streptococcus viridans* to some antibiotics used for prophylaxis of IE.
- The modifications in the prevalence of germs causing IE worldwide, and also in Argentina, particularly the increasing role of *Staphylococcus aureus* among Gram positive cocci.
- The estimated preventive fraction of IE is lower than the risk of anaphylaxis secondary to the administration of beta lactams.
- Finally, the indiscriminate use of antibiotics leads to higher resistance to antimicrobial agents, which constitutes an emerging Public Health issue that should not be ignored.

Antibiotic prophylaxis is recommended to prevent an endovascular infection before a high-risk procedure is performed (Table 1) in patients with cardiac conditions at high risk of infective endocarditis (Table 2). Class I, level of evidence C.

Table 1. Recommendations for prophylaxis of infective endocarditis according to the type of procedure and antibiotics recommended

Procedure	Antibiotics in adults		Antibiotics in children
<ul style="list-style-type: none"> • Manipulation of the gingival or periapical region of the teeth • Perforation of the oral mucosa 	Amoxicillin or ampicillin 2g orally or IV 30-60 minutes before the procedure	For penicillin-allergic patients: clindamycin 600 mg orally or IV 30-60 minutes before the procedure	Amoxicillin or ampicillin 50 mg/kg orally or IV Single dose
<ul style="list-style-type: none"> • Tonsillectomy • Adenoidectomy 	Amoxicillin or ampicillin 2g orally or IV 30-60 minutes before the procedure	For penicillin-allergic patients: clindamycin 600 mg orally or IV 30-60 minutes before the procedure	For penicillin-allergic patients: clindamycin 20 mg/kg orally or IV 30-60 minutes before the procedure Single dose

Table 2. Cardiac conditions in which prophylaxis of infective endocarditis should be indicated

<ul style="list-style-type: none"> • Patients with any prosthetic valve or any prosthetic material used for cardiac valve repair • Patients with previous infective endocarditis • Patients with congenital heart defects: <ol style="list-style-type: none"> a. Any type of unrepaired cyanotic congenital heart defect or with underlying defects after its repair, including palliative shunts and conduits b. Completely repaired congenital heart defect with prosthetic material or device, placed by surgery or percutaneous intervention, during the first 6 months after the procedure c. Repaired congenital heart defect with persisting residual defect at the site of prosthetic patch or device positioning, whether placed by surgery or by percutaneous intervention
