Protocol

Treating endocarditis: a protocol from a middle-income country

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The following protocol is intended to be a useful and practical guide to empirical and pathogen directed antimicrobial therapy of infective endocarditis (IE) in adult patients. It has been in use for a number of years at the Instituto Nacional de Cardiologia, a referral center for cardiac surgery located in Rio de Janeiro, Brazil. The institute belongs to the national health system and annually, approximately 270 valve replacement surgeries in adults are performed; there are 8000 outpatient visits to the Heart Valve Disease Department, and 25 cases of definite IE according to the modified Duke criteria in adults are admitted. Around 2/3 of patients referred for surgery are from other hospitals.

The protocol has been updated regularly, with incorporation of the relevant published literature; the last update was on May 2018. The main sources used were the British guidelines (Gould et al., 2012), the American guidelines (Baddour et al., 2015) and the European guidelines (Habib et al., 2015), but several other references provided evidence for its construction.

1.Collecting blood cultures

Blood cultures must be collected by peripheral vein puncture. The protocol used is as follows:

A) The patient is stable, and has not used antibiotics previously:
Draw 20 ml of blood at moments 0, 1 hour and 6 hours. Use for the first set an aerobic and one anaerobic bottle per set, and in the third set, 2 aerobic bottles. Do not start antibiotics yet. If blood cultures remain negative after 72 hours, collect another 4 bottles and at the same time, collect blood for *Bartonella spp* and *Coxiella burnetii* serologies and polymerase chain reaction (PCR). Start empirical treatment then.

B) If the patient is stable but is on antibiotics, we recommend these are stopped for at least 72 hours (ideally for 1 week). After this time, collect 6 blood culture bottles (two at 0, two at 1 hour and two at 6 hours, as described in A).

C1) The patient is unstable, and has not used antibiotics: collect 4 bottles (2 sets), with a 30 minute interval between them. Start empirical treatment taking into account whether the patient has an acute onset of signs and symptoms (usually of days, certainly less than a month) or a subacute onset (more than 4 weeks of the start of signs and symptoms), if it is a native valve endocarditis or prosthetic valve IE and whether the patient has been exposed to healthcare (see below).

C2) The patient is unstable, and is on antibiotics: keep the antibiotics and collect blood cultures immediately, as in C1 (4 bottles in total, with a 30 minute interval). Discuss antibiotic change with the infectious diseases specialist.

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2.Echocardiogram
Organize a transthoracic echocardiogram (TTE) if IE involves native valves, and a transesophageal echocardiogram if IE involves prosthetic valves, intracardiac devices, if there is atrioventricular block or if TTE has not been helpful.

3.Other important investigations
Full blood count, C-reactive protein levels, erythrocyte sedimentation rate (ESR), renal function, routine electrolytes, urinalysis, tomographic scans of the brain and abdomen if IE is left- sided.

4.intravenous access
If the diagnosis of IE is definite or probable, and the patients will be treated as such, consider early the insertion of a *peripherally inserted central catheter* (PICC). PICCs are the type of intravenous line that have been associated with less adverse events and that have the longer duration of routinely used IV access in the scenario of antibiotic treatment of IE, potentially lasting weeks if adequately cared for.

Antimicrobial Treatment
Infective endocarditis requires surgical treatment when left-sided in around 40 to 50% of patients. Therefore, antimicrobial treatment is just a part of the treatment strategy. Though IE is a severe infection, response to antimicrobials usually occurs in 3 to 5 days. Therefore, failure to respond to antimicrobial treatment usually indicates complications such as perivalvular abscess, intra-abdominal abscess, problems with intravenous lines or antibiotic hypersensitivity.

The following are treatment guidelines used in our institution:

Native valve or late-onset prosthetic valve IE with a subacute course

"Subacute" defined as that situation where signs and symptoms have developed insidiously over more than 4 weeks.

Empirical treatment:

Scenario A: Patients younger than 50 years of age and that do not have recent exposure to healthcare related procedures (for example, central venous catheters, gastrointestinal or genitourinary procedures).

Ampicillin 2 g IV 4 -hourly

Rationale: coverage for *viridans* group streptococci. Greater commercial availability of ampicillin than of penicillin.

Empirical treatment:

Scenario B: Patients older than 50 years and/or with a recent exposure to healthcare (such as central venous catheters, gastrointestinal or genitourinary procedures), or men with prostatic disease.

Ampicillin 2 g IV 4- hourly + Gentamicin 3mg/kg IV once a day

In case *viridans* group streptococci are confirmed:

a)If the patient will be submitted to cardiac surgery: maintain ampicillin and stop gentamicin. Gentamicin should be continued **only if** there is intermediate resistance to penicillin, defined as an MIC between 0.12 and 0.5 mcg/ml. In this case, it will be maintained as a once daily infusion, for 2 weeks.
If the patient has uncomplicated viridans group IE, that is, no valvular dysfunction, no abscess and no embolic lesions, the total duration of combined ampicillin and gentamicin treatment will be 2 weeks .
b)If the patient will not undergo surgery: keep ampicillin and gentamicin.
The goal of associating gentamicin is to shorten the duration of IE treatment. However, if the patient has a surgical indication, the infectious focus of infection will be removed, and duration of treatment will be decided according to the macroscopic surgical findings as well as the histopathology of the excised valve. Stopping gentamicin will avoid further kidney injury. Kidney dysfunction occurs in around 33% of patients with IE and post valve replacement surgery hemodialysis is necessary for 10% .
c)When the patient is discharged from the cardiac postoperative unit to the ward, change ampicillin to ceftriaxone 2 grams once daily, till the completion of antibiotic treatment.

In case *Enterococcus* is confirmed:

Check for aminoglycoside resistance and confirm if gentamicin may be used.
If the patient is to have cardiac surgery: keep ampicillin, stop gentamicin and start ceftriaxone 2 grams every 12 hours instead.
If the patient is not surgical: keep gentamicin for 2 to 3 weeks in patients with native valve IE, associated to ampicillin (which will be kept for 4 to 6 weeks).
Alternatively, ampicillin may be associated with ceftriaxone all along the course of treatment (6 weeks in all).
In patients with prosthetic valve enterococcal IE who will be treated conservatively, caution is recommended: use gentamicin 1 mg/kg 8- hourly and treat for 6 weeks.

If blood cultures are negative:

Scenario A: **keep Ampicillin.**

Scenario B: keep **Ampicillin + Gentamicin or Ampicillin +Ceftriaxone**

If epidemiology is suggestive of zoonotic agents as below:

1.Direct or indirect contact with farm animals or their products, such as ingestion of raw milk or cheese, and especially if proximity in the last weeks to a parturient mammal suggests *Coxiella burnetii* and contact with cats suggests *Bartonella* spp,

2. The patient did not use antimicrobials before blood cultures were drawn and they are negative after a 7 -day incubation period,

Change regime to ceftriaxone 2 g/day (6 weeks) + gentamicin 3mg/kg/day in one single daily dose (2 weeks) + doxycycline 100 mg PO twice a day (6 weeks)

Rationale: *Bartonella* spp, *Coxiella* and HACEK are possible etiologic agents. Send away blood for *Coxiella burnetii* and *Bartonella* serologies. It is very important to establish diagnosis as treatment for *Coxiella* is long, around 18 months and association with chloroquine is recommended.

Native valve or late- onset prosthetic valve IE with an acute course

"Acute" defined as that situation where signs and symptoms have developed abruptly and usually over days, but less than 4 weeks.

Empirical treatment:

Oxacillin 2 g 4- hourly + Vancomycin 15 to 20 mg/kg 12- hourly

Important: The patient needs to be weighed so that the correct dose is given. THE LOADING DOSE OF VANCOMYCIN IS 25 MG/KG.

Rationale: Coverage for methicillin sensitive (MSSA) and resistant *S. aureus* (MRSA).

Further action:

- Stop vancomycin when blood culture results are available (usually after 48 to 72 h) if MSSA is isolated;
- If the patient has a prosthesis and MSSA is isolated, associate gentamicin once daily with the dose of 3 to 5 mg/kg for 2 weeks, and rifampin 300mg PO 8 hourly (after 5 days of oxacillin) for the whole course of treatment;
- If MRSA is isolated, stop oxacillin and keep vancomycin;
- If MRSA is isolated and the patient has a prosthesis, associate gentamicin once daily with the dose of 3 to 5 mg/kg for 2 weeks, and rifampin 300mg PO 8 hourly (after 5 days of vancomycin) for the whole course of treatment;
- After the 3rd dose of vancomycin, pre-dose serum levels must be checked and dose adjusted according to protocol.

- If MRSA is isolated and there are any of the following: vancomycin MIC >1.5, moderate to severe renal dysfunction (creatinine clearance, CrCl, between 30 and 50 ml/min) and vancomycin allergy

use Daptomycin 8 to 10 mg/kg IV once daily

- If the CrCl is < 30 ml/min or the patient is on hemodialysis, give daptomycin at an attack dose of 10 mg/kg and then use 4 mg/kg/day once daily.

- If daptomycin is used for native valve IE, consider associating oxacillin or gentamicin or ceftaroline (please consult infectious disease specialist).
- If daptomycin is used for prosthetic valve IE, associate gentamicin **and** rifampin.
- If blood cultures remain negative in this acute scenario, consult ID specialist and discuss the case individually.

Acute onset of infective endocarditis affecting a recently implanted valve prosthesis

Empirical treatment if diagnosis of IE occurs within 2 months of valve implantation:
Vancomycin 15 mg/kg 12 hourly + Gentamicin 3 mg/kg/day as a single daily dose + Meropenem 1 g 8-hourly + equinocandin IV

Add rifampicin 300 mg PO 8 hourly after 5 days.

Empirical treatment if diagnosis of IE occurs more than 2 months and less than 1 year of valve implantation:

Vancomycin 15 mg/kg 12 hourly + Gentamicin 3 mg/kg/day as a single daily dose

Add rifampicin 300 mg PO 8 hourly after 5 days

Important: The patient needs to be weighed so that the correct dose is given. The loading dose of vancomycin is 25 mg/kg.
After the 3rd dose, pre -dose serum levels of vancomycin must be done and dose adjusted according to protocol.
Rationale: coverage for coagulase negative staphylococci, for MRSA, for enterobacteria that are extended spectrum lactamase (ESBL) producers and for *Candida* spp when valve replacement has occurred less than 2 months. Starting rifampin after 5 days is to minimize the risk of staphylococci developing resistance.
It is very important to draw blood cultures specifically for fungi, as *Candida* spp may grow in usual culture media but may take longer to do so and the yield is not optimal. If available, ask for serum β (1-3)-glucan.
Consult with the ID specialist for therapeutic adjustment of antimicrobials when a pathogen has been isolated. For non-resistant Gram negative organisms, preference will be given to the use of a β-lactam combined with an aminoglycoside.
If *Candida spp*, is isolated, liposomal amphotericin B (3-5mg/Kg/day) or an equinocandin (caspofungin, anidulafungin or micafungin) may be used; discuss with the ID specialist.
If blood cultures are negative, keep vancomycin, gentamicin and rifampin, and consider maintaining antifungal therapy (consult ID).

Post-operative antibiotics for IE

General rules

1)Do not send valves for cultures, except in blood culture negative endocarditis. Send all surgical specimens for histopathology (HP).
2)Use, as a gold standard, histopathology of valves to guide antibiotic duration following valve replacement surgery. Results should be available 1 week after surgery.
3)Culture results should be obtained in BCNE but sensitivity of valve culture is low, around 15%. Also, there may be a problem with false positive results in valve culture. If the same organism is grown from valve and blood, keep antibiotics for 4 weeks post-surgery.

WHAT TO DO FOR NATIVE VALVE IE, considering Gram positive cocci or HACEK group pathogens the probable agents:

a)If valve HP shows active IE (presence of neutrophils and bacteria) treat for 4 weeks postsurgery. If the agent has been identified otherwise as *viridans* or *bovis* group streptococci, treat for 2 weeks post-operatively (total duration of treatment will be 4 weeks).

b)If valve HP shows active IE but no bacteria, treat for around 2 weeks (total duration of 4 to 6 weeks for staphylococci, 6 weeks for enterococci and 3 to 4 weeks for *viridans* or *bovis* group streptococci).

c)If surgical findings show destructive IE, with features such as perivalvular abscess, disinsertion, fistulae or leaflet perforation, total antibiotic duration should not be less than 6 weeks.

d)If the clinical features of IE have evolved for more than 6 months, treat for 4 to 6 weeks total time. Pay close attention to embolic lesions to the central nervous system, spleen, mycotic aneurisms of peripheral arteries and adjust the timing and dosing of antimicrobials accordingly.

e)If HP findings show resolved IE, withdraw antibiotics.

-Duration of antibiotic treatment for fungi and Gram negative organisms will be decided on a case- by- case basis.

Other recommendations:

Gentamicin:

- Gentamicin must be diluted and infused over 45 minutes to avoid risk of muscle paralysis.
- Weigh the patient and calculate the dose; use the real weight except if body mass index (BMI) is >30, when ideal body weight should be used;
- Check pre-dose levels of gentamicin prior to the second dose;
- Desirable pre-dose serum levels are 1 to 1.5 mcg/ml;
- Monitor serum levels once weekly in stable patients, and twice weekly in unstable ones. Correct the dose according to protocol.

Vancomycin

- Vancomycin must be diluted and infused over at least one hour to avoid the red man syndrome and to minimize the risks of phlebitis
-Check pre-dose serum levels one hour before the 4th dose;
- Monitor serum levels once weekly in stable patients, and twice weekly in unstable ones. Correct the dose according to protocol.
-Doses above 4 grams per day are associated with considerable chance of nephrotoxicity and alternative treatment with daptomycin should be considered.

Daptomycin

- Patients using daptomycin should have creatine phosphokinase (CPK) levels checked once a week.
- CPK levels should also be checked if the patient complains of myalgia.
- CPK levels > 1000 IU/L (5 times the upper limit of normal) in a patient with myalgia or muscle weakness, or > 2000 IU/L irrespective of symptoms, are considered high. In these cases, daptomycin must be stopped.

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References

1. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications Circulation 2015; 132: 1435–86.
2. Brandao TJ, Januario-da-Silva CA, Correia MG, Zappa M, Abrantes JA, Dantas AM, et al. Histopathology of valves in infective endocarditis, diagnostic criteria and treatment considerations. Infection 2016; 45: 199-207.
3. Carugati M, Bayer A, Miro JM, Park LP, Guimaraes AC, Skoutelis A, et al. High-dose daptomycin therapy for left-sided infective endocarditis:a prospective study from the international collaboration on endocarditis. Antimicrob Agents Chemother 2013; 57: 6213-22.
4. Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutin E, Karchmer AW, Rupp ME, et al. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009; 48: 713-21.
5. De Paula DH, Tura BR, Lamas CC. Adverse events related to intravenous antibiotic therapy: a prospective observational study in the treatment of infective endocarditis. BMJ Open 2012; 2. pii: e001189. doi: 10.1136/bmjopen-2012-001189.
6. Dohmen PM, Guleri A, Capone A, Utili R, Seaton RA, Gonzalez-Ramallo VJ, et al. Daptomycin for the treatment of infective endocarditis: results from a European registry. J Antimicrob Chemother 2013; 68: 936–42.
7. Fernandez-Hidalgo N, Almirante B, Gavalda J, Gurgui M, Pena C, de Alarcon A, et al. Ampicillin plus ceftriaxone is as effective as ampicillin plus gentamicin for treating Enterococcus faecalis infective endocarditis. Clin Infect Dis 2013; 56: 1261-8.
8. Gould FK, Denning DW, Elliott TS, Foweraker J, Perry JD, Prendergast BD, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2012; 67: 269-89.
9. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC guidelines for the management of infective endocarditis. Eur Heart J 2015; 36: 3075–128.
10. Janson B , Thursky K. Dosing of antibiotics in obesity. Curr Opinion Infect Dis 2012; 25: 634-49.
11. Kemp CD, Arnaoutakis GJ, Geroge TJ, Smith MA, Patel ND, Cameron DE, et al. Valve surgery for infective endocarditis is associated with high hospital charges. J Heart Valve Dis 2013; 22: 110-7.
12. Kullar R, McClellan I, Geriak M, Sakoulas G. Efficacy and safety of daptomycin in patients with renal impairment: a multicenter retrospective analysis. Pharmacother 2014; 34: 582-9.

13. Legrand M, Pirracchio R, Rosa A, Peterson ML, Van der Laan M, Fabiani JN, et al. Incidence, risk factors and prediction of post-operative acute kidney injury Heart Vessels and Transplantation 2018; 2: doi:
following cardiac surgery for active infective endocarditis: an observational study. Crit Care 2013; 17: R220.

14. Liu C, Bayer E, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et a . Clinical Practice Guidelines by the Infectious Diseases Society of America for the treatment of Methicillin-resistant Staphylococcus aureus in adultsand children. Clin Infect Dis 2011:1-38.

15. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidente of nephrotoxicity. Antimicrob Agents Chemother 2008; 52: 1330-6.

16. Machado MN, Nakazone MA, Murad-Junior JA, Maia LN. Surgical treatment for infective endocarditis and hospital mortality in a Brazilian single-center. Rev Bras Cir Cardiovasc 2013; 28: 29-35.

17. McConeghy KW, Bleasdale SC, Rodvold KA. The empirical combination of vancomycin and a β-lactam for Staphylococcal bacteremia. Clin Infect Dis 2013; 57: 1760-5.

18. Mueller BA, Crompton JA, Donovan BJ, Yankalev S, Lamp KC. Safety of daptomycin in patients receiving hemodialysis. Pharmacother 2011; 31: 665-72.

19. Munoz P, Giannella M, Scoti F, Predomingo M, Puga D, Pinto A, et al. Two weeks of postsurgical therapy may be enough for high-risk cases of endocarditis caused by Streptococcus viridans or Streptococcus bovis. Clin Microbiol Infect 2012; 18: 293-9.

20. Pappas P, Kauffman C, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48: 503–35.

21. Pericas JM, Cervera C, Moreno A, Garcia-de-la-Maria C, Almela M, Falces C, et al. Outcome of Enterococcus faecalis infective endocarditis according to the length of antibiotic therapy: Preliminary data from a cohort of 78 patients. PLoS One 2018; 13: e0192387.

22. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the Amercian Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009; 66: 82-98.

23. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother 2013; 57: 734-44.

24. Wong WT, Choi G, Gomersall CD, Lipman J. To increase or decrease dosage of antimicrobials in septic patients during continuous renal replacement therapy: the eternal doubt. Curr Opin Pharmacol 2015; 24: 68-78.