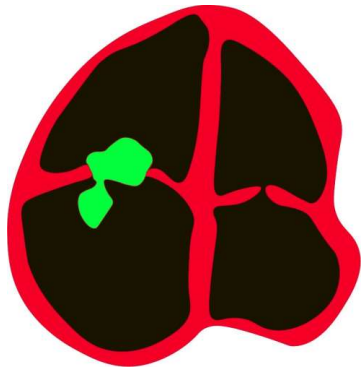


Blood Culture Negative Infective Endocarditis: Recent Updates on Changing Clinical Entity



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Definition

- Blood Culture Negative Infective Endocarditis (BCNIE) refers to infective endocarditis in which no causative microorganism can be grown using the usual blood culture methods following inoculation of at least three independent blood samples in a standard blood culture system with negative cultures after five days of incubation and subculturing.
- *Baddour LM et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435-1486.*
- *Raoult D, Casalta JP, Richet H, Khan M, Bernit E, Rovey C, Branger S, Gouriet F, Imbert G, Bothello E, Collart F, Habib G. Contribution of systematic serological testing in diagnosis of infective endocarditis. J Clin Microbiol. 2005;43(10):5238.*

Epidemiology

- A European study included 820 cases indicated 20% of patients with confirmed IE had negative blood cultures.
- ESC confirmed the incidence may vary up to 31%.

Werner M, Andersson R, Olaison L, Hogevik H. A clinical study of culture-negative endocarditis. Medicine (Baltimore). 2003;82:263-273. DOI: 10.1097/01.md.0000085056.63483.d2

Etiology

- Administration of antimicrobial agents before blood culture.
- Improper blood collection technique.
- Endocarditis related to fastidious microorganisms in which prolonged incubation is necessary.
- True blood culture-negative endocarditis, due to intra-cellular bacteria that cannot be detected by currently available routine blood culture system.
- Non-infective endocarditis due to systemic disease.

Common organisms causing BCNE

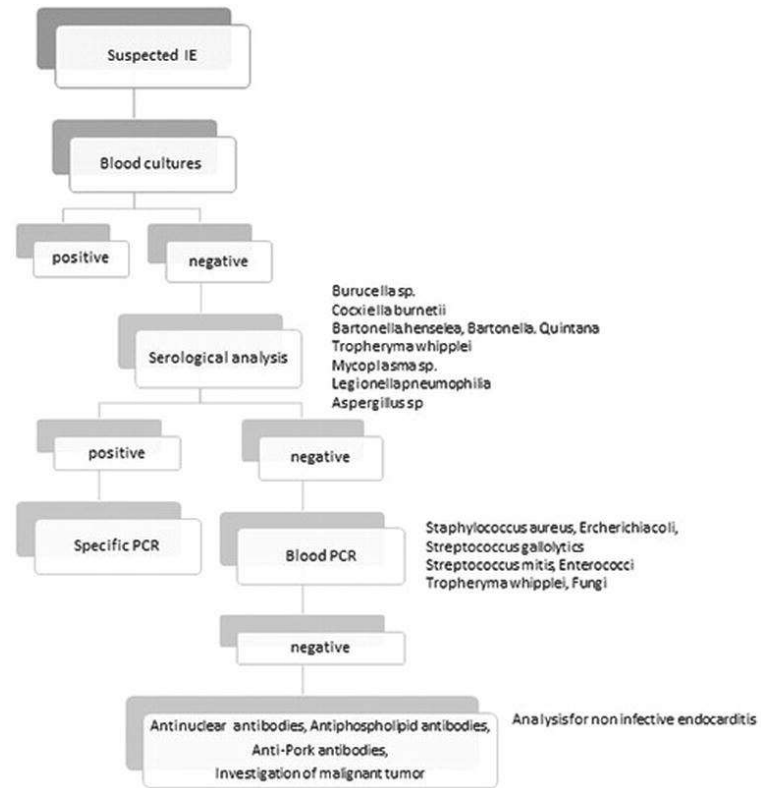
- *Coxiella burnetii*
- *Bartonella* spp.
- *Mycoplasma pneumoniae*
- *Brucella* spp.
- *Legionella pneumophila*
- *Tropheryma whippelii*
- *Bartonella* spp
- *Streptococcus gallolyticus*
- *Streptococcus mitis*
- Enterococci
- *Staphylococcus aureus*
- *Escherichia coli*
- and fastidious bacteria

Blood Culture technique

- No prior antibiotic
- Aseptic technique
- Sterile container (Blood culture bottles)
- 3 specimens of blood at an interval of 30 min
- Immediate transport or in case of delay specimen must be incubated and must not refrigerated



Approach to BCNE



Additional tests to be Performed

Pathogen	Diagnostic procedures
Brucella sp.	blood cultures, serology, immunohistology, PCR of surgical materials
Coxiella burnetii	serology (IgG phase I >1:800, tissue culture, immunohistology, PCR of surgical materials
Bartonella sp.	blood cultures, serology, culture, immunohistology, PCR of surgical materials
Tropheryma whippelii	histology and PCR of surgical materials
Mycoplasma sp.	serology, culture, immunohistology, PCR of surgical materials
Legionella sp.	blood cultures, serology, culture, immunohistology, PCR of surgical materials
Fungi	blood cultures, serology, immunohistology, PCR of surgical materials

Tests to detect Systemic Disease

Tests	Disease
ANA	SLE
Anti phospholipid Antibody	Antiphospholipid antibody syndrome
Anti pork Antibody	
Malignancy screening	Malignancy

Treatment

- Patients with BCNIE are often treated empirically for the more common bacterial causes of IE during the waiting time.
- Consultation with an ID specialist to define the most appropriate choice of therapy is recommended.
- Once additional clinical and laboratory data were brought, initial empirical therapy should be changed to more specific treatment

Native Valve BCNIE

- Patients with acute (days) clinical presentations of native valve infection, empirical coverage could include vancomycin and cefepime as an initial regimen.
- For patients with a subacute (weeks) presentation of native valve IE, one treatment option could include vancomycin and ampicillin-sulbactam .

Fournier PE, Gouriet F, Casalta JP, et al. Blood culture-negative endocarditis: Improving the diagnostic yield using new diagnostic tools. Medicine (Baltimore). 2017;96(47):e8392. doi:10.1097/MD.0000000000008392

Prosthetic Valve BCNIE

- For patients with culture-negative prosthetic valve IE, A regimen could include vancomycin, rifampin, gentamicin .
- If symptom onset is >1 year after valve placement, one initial treatment option could include vancomycin and ceftriaxone.

Fournier PE, Gouriet F, Casalta JP, et al. Blood culture-negative endocarditis: Improving the diagnostic yield using new diagnostic tools. Medicine (Baltimore). 2017;96(47):e8392. doi:10.1097/MD.00000000000008392

Special Situations

Table 19 Antibiotic treatment of blood culture-negative infective endocarditis (adapted from Brouqui et al.¹⁹³)

Pathogens	Proposed therapy ^a	Treatment outcome
<i>Brucella</i> spp.	Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300–600/24 h) for ≥3–6 months ^b orally	Treatment success defined as an antibody titre <1:60. Some authors recommend adding gentamicin for the first 3 weeks.
<i>C. burnetii</i> (agent of Q fever)	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) ^c orally (>18 months of treatment)	Treatment success defined as anti-phase I IgG titre <1:200, and IgA and IgM titres <1:50.
<i>Eartonella</i> spp. ^d	Doxycycline 100 mg/12 h orally for 4 weeks plus gentamicin (3 mg/24 h) i.v. for 2 weeks	Treatment success expected in ≥90%.
<i>Legionella</i> spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 weeks or clarithromycin (500 mg/12 h) i.v. for 2 weeks, then orally for 4 weeks plus rifampin (300–1200 mg/24 h)	Optimal treatment unknown.
<i>Mycoplasma</i> spp.	Levofloxacin (500 mg/12 h) i.v. or orally for ≥6 months ^e	Optimal treatment unknown.
<i>T. whipplei</i> (agent of Whipple's disease) ^f	Doxycycline (200 mg/24 h) plus hydroxychloroquine (200–600 mg/24 h) ^c orally for ≥18 months	Long-term treatment, optimal duration unknown.

ID = infectious disease; IE = infective endocarditis; Ig = immunoglobulin; i.v. = intravenous; U = units.

^aOwing to the lack of large series, the optimal duration of treatment of IE due to these pathogens is unknown. The presented durations are based on selected case reports. Consultation with an ID specialist is recommended.

^bAddition of streptomycin (15 mg/kg/24 h in 2 doses) for the first few weeks is optional.

^cDoxycycline plus hydroxychloroquine (with monitoring of serum hydroxychloroquine levels) is significantly superior to doxycycline.¹⁹⁴

^dSeveral therapeutic regimens have been reported, including aminopenicillins (ampicillin or amoxicillin, 12 g/24 h i.v.) or cephalosporins (ceftriaxone, 2 g/24 h i.v.) combined with aminoglycosides (gentamicin or netilmicin).¹⁹⁵ Dosages are as for streptococcal and enterococcal IE (Tables 16 and 18).^{196,197}

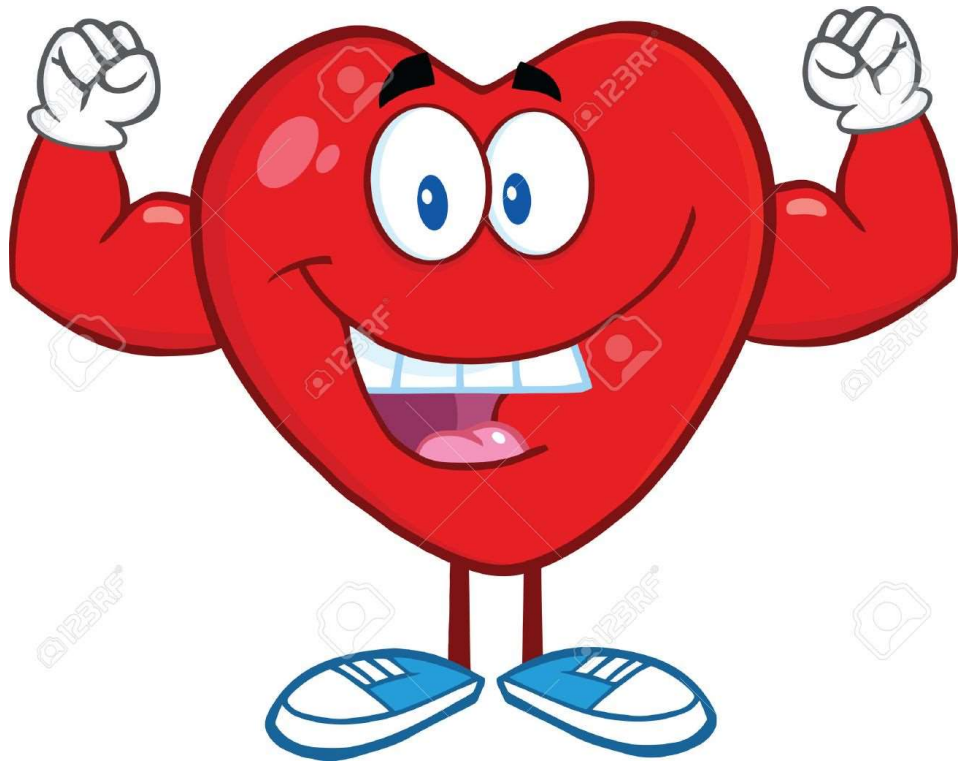
^eNewer fluoroquinolones (levofloxacin, moxifloxacin) are more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma* spp., *Legionella* spp., and *Chlamydia* spp.

^fTreatment of Whipple's IE remains highly empirical. In the case of central nervous system involvement, sulfadiazine 1.5 g/6 h orally must be added to doxycycline. An alternative

Fungal Endocarditis

- Fungal endocarditis treatment should include both medical and surgical therapy.
- Amphotericin B should be the drug of choice . Other options include the addition of flucytosine to amphotericin B, or Echinocandin. Suppressive longterm treatment with oral azoles (fluconazole for *Candida* and voriconazole for *Aspergillus*) is recommended.





“Keep your patients heart healthy and then sleep with a happy heart”

Take Home Message

- Keeping IE as a suspicion IN PROPER TIME
- Proper blood culture technique; Maintain sterility
- Judicious use of antibiotic
- Exclude systemic disease

Conclusion

Blood culture-negative endocarditis is still a clinical challenge with heterogeneous pathology.

Team approach including cardiologists, infectious disease specialists, microbiologists and immunologist is crucial for the correct diagnosis that is able to reach rapidly the new diagnostic microbiological techniques, and high-quality epidemiological information.

