DIAGNOSIS OF PATIENTS WITH

Infective Endocarditis

Infective endocarditis (IE), an infection of the endothelial surface of the heart (endocardium), has not escaped the impact of burgeoning antibiotic resistance among common pathogens like most other bacterial infections[1]. 50% of IE cases carries poor prognosis and may develop in patients with no history of valve disease[2], it is therefore imperative to remain vigilant to the possibility of diagnosis in patients especially those with febrile illness and heart conditions.

The normal valve endothelium is resistant to colonization and infection by circulating bacteria due to constant blood flow. The etiology of endocarditis is typically by two underlying factors:

1. Mechanical disruption of the endothelium
2. Endothelial inflammation

The characteristic lesion of IE is a vegetation, a meshwork of platelets and fibrin enmeshed at the damaged endocardium or heart valves[1]. Causative IE pathogens may colonize the vegetation and escape the host defence system. Endocarditis occurs.

Fibrin Mesh

Microorganism

Endocardial Vegetations

Fragments of infected vegetation may then break off, travel through the blood vessels to distant parts of the body and eventually inducing problems like stroke or tissue damage where blood flow is obstructed. Moreover, IE may also develop on heart implants such as artificial heart valves, pacemakers, or defibrillators[3]. Damaged infected valves can cause severe leaking (regurgitation) of blood back through the valves, leading to intractable congestive heart failure and myocardial abscesses. If left untreated, IE is generally fatal. Of note, IE does not occur only after invasive procedures, but could also be a consequence of chewing and tooth brushing[3].

Diagnosis of IE is usually based on clinical, microbiologic and echocardiographic findings. However, IE is not a uniform disease and the epidemiological profile varies highly by different forms. For this reason, IE requires a collaborative approach and early involvement of cardiologist, microbiologist, infection disease specialist with a high index of vigilance to guide investigation[1,3].

Staphylococci and streptococci account predominantly for 80% of IE cases[2], acute IE is typically caused by *staphylococcus aureus*, whereas the subacute variety can be caused by *streptococci viridans*, *enterococci, coagulase-negative staphylococcus* and *Gram-negative coccobacilli.* Of which, 10% of culture-negative IE cases could reflect patients exposed to antibiotic agents before diagnosis or IE caused by fastidious microorganisms such as Gram-negative bacilli of the HACEK group[3]. Up to 90% of patients are present with low grade fever and non-specific symptoms which may thwart initial assessment. Heart murmurs are found in 35% patients[4].
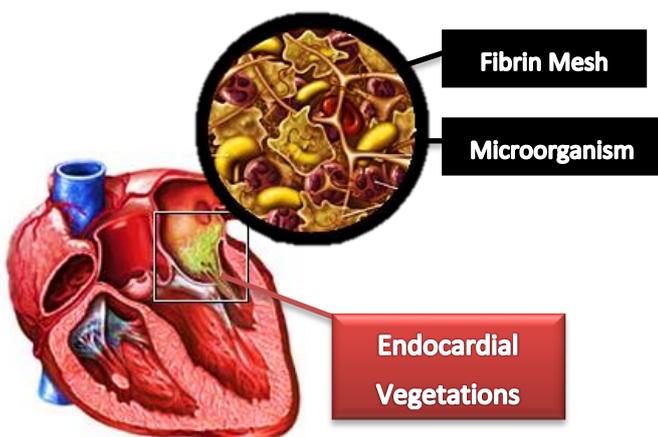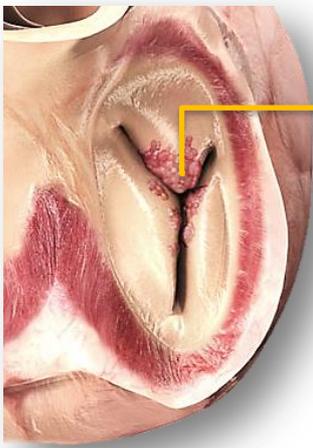
Endocarditis on Tricuspid Valve

" *Positive blood cultures remain the cornerstones of diagnosis and provide live bacteria for susceptibility testing.* "

In IE, bacteremia is almost constant, thus positive blood cultures remain the cornerstones of diagnosis[3]. The need for culture prior to antibiotic administration is self-evident, but more often than not contemporary practice reveals violation of this rule, inflicting serious ramifications for diagnosis and treatment efficacy.

According to the CLSI approved guideline for blood culture[5], patients with suspected IE or other endovascular infections (e.g. catheter-related) will require three blood culture sets to be drawn at intervals, each containing 10mL of blood obtained using meticulous aseptic technique by venipuncture, to document continuous bacteremia. If those sets are negative at 24 hours, obtain 2 or more culture sets for a cumulative of 5 sets overall.

The continuous nature of most IE-associated bacteremias renders timing less important, hence there is no rationale for delaying blood sampling to coincide with peaks of fever. Cockerill's study[6] in 2004 reported that the cumulative yield of pathogens from IE patients was 90% from the first blood culture taken – the diagnostic yield of repeated sampling thereafter maybe lower. Sampling from central venous catheters should be avoided in view of high risk of contaminants (typically staphylococcal) and misleading conclusions.

For acute IE cases that may be caused by highly virulent pathogens such as *staphylococcus aureus*, blood culture sets should be drawn immediately and within a 30-minute period before administration of empiric antimicrobial agents[5]. For subacute IE cases, there is no urgent need to obtain blood cultures before initiation of empiric therapy. For these patient cases, it is far more important in the attempt to establish the microbiological diagnosis. CLSI[5] suggests that blood culture collections be spaced 30 minutes to 1 hour apart to help document continuous bacteremia that may provide more clinical value, especially if the echocardiogram is negative or equivocal. Taking only a single blood culture should be regarded cautiously and may not be sufficient as it would not enable determination of continuous bacteremia, no distinction of contamination and true bacteremia, and surely would not provide the appropriate volume.

Although there is low prevalence of IE caused by anaerobes, the use of an anaerobic culture complements the aerobic media in the recovery of facultative anaerobes, especially the nutritionally variant streptococci, and as such should still be included with every blood culture set[3, 5].

All episodes of IE detected within a 5-day period of culture incubation were evinced by recent data from the Mayo Clinic. When culture sets remain negative at 5 days, subculture on chocolate agar plates may allow identification of fastidious organism. In Baron's study[7], extended incubation in 215 IE patients showed only recovery of minimal less clinically relevant organisms (*Mycobacterium avium complexes, Legionella pheumophila*). In the same study, all HACEK microorganisms were recovered within 5 days, hence prolonged incubation period is unnecessary.

Coupled with the inevitable misuse of antibiotic, this has resulted in an overall worsening of the average clinical course of patients with IE. Therefore using resin-supplemented culture medium formulation will better improve the overall recovery of microorganisms from IE patients[5] by antibiotic neutralization.

Table I   Modified Duke criteria for the diagnosis of infective endocarditis (adapted from Li et al.[94])

MAJOR CRITERIA

Blood cultures positive for IE:

- Typical microorganisms consistent with IE from two separate blood cultures:
  Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or
  Community-acquired enterococci, in the absence of a primary focus;

  or
- Microorganisms consistent with IE from persistently positive blood cultures:
  At least two positive blood cultures of blood samples drawn > 12 h apart; or
  All of three or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)

  or
- Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer > 1 : 800

Evidence of endocardial involvement

- Echocardiography positive for IE
  Vegetation - Abscess - New partial dehiscence of prosthetic valve
- New valvular regurgitation

MINOR CRITERIA

- Predisposition: predisposing heart condition, injection drug use
- Fever: temperature > 38°C
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhages, conjunctival haemorrhages, Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion or serological evidence of active infection with organism consistent with IE

Diagnosis of IE is definite in the presence of	Diagnosis of IE is possible in the presence of
2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria	1 major and 1 minor criteria, or 3 minor criteria

Adapted from Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;**30**:633–638.

Due to technological advances such as intravenous catheterization & implants, fungal IE caused by yeasts and molds is not under initial considerations until the routine blood cultures are reported as negative. In such instances, fungal media is requested. The most common fungal pathogens implicated are *Candida albicans* and non-*albicans Candida* spp[5]. Many of the same technical factors for diagnosis of bacterial IE apply to the diagnosis of fungal endocarditis. In short, if optimal methods are utilized, the positivity of blood cultures in fungal endocarditis can range from 83 to 95%[5].

For the diagnosis criteria of infective endocarditis, clinical variability and complexity in IE dictate that the guidelines available in the context of IE be used to support and not supplant physician-directed decisions in individual patient management. The modified DUKE criteria[8] based upon clinical, echocardiographic, and microbiological findings by blood culture provide high sensitivity and specificity (80% overall) for the diagnosis of IE (Table 1). It is therefore imperative that optimal culture techniques are used to promise positivity & recovery in over 90% of IE cases for patient survival.

Image source :

I.   http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/TheImpactofCongenitalHeartDefects/ Infective-Endocarditis_UCM_307108_Article.jsp
II.   http://www.heartupdate.com/infections/infective-endocarditis-duke-diagnostic-criteria_396/

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[8] **Li JS et al. (2000).** Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*;30:633–638.