Infective Endocarditis: Riskfactors, Diagnosisand Prevention

MurtazaMustafa[1], MPhanidranath[2], ELIllzam[3], MI.Hashmi[4], AM.Sharifa[5], MM.SEIN[6]

[1,2,6]Facultyof Medicine and Health Sciences,University Malaysia,Sabah,Kota Kinabalu,Sabah.Malaysia.
[3]Clinic Family Planning Association,Kota Kinabalu,Sabah,Malaysia.
[4]Facultyof Food Science and Nutrition,University Malaysia,Sabah,Kota Kinabalu,Sabah,Malaysia
[5]. Quality Unit, Hospital Queen Elizabeth,Kota Kinabalu,Sabah,Malaysia.

Abstract:*Infective Endocarditis (IE) is the infection of oneor more heart valves. Clinical symptoms vary from patient to patient, and can be acute or subacute. Increased incidence in patient with advance age and with predisposingfactors for IE.Frequent symptoms include:fever,heart murmur,vascular phenomena,immunologic phenomena, rheumatic heart disease,congenital heart disease, mitral valve prolapse, and heath care associated endocarditis. Diagnosis of IE by revised Duke criteria,pathologic,clinical,major and minor criteria to make a definite IE diagnosis. Treatment options being the high dose antibiotics e.g.,vancomycin and ceftriaxone for 2 to 6 weeks by theIV route to maximize diffusion of antibiotics into the vegetation(s). Microbial susceptibility with identification, MIC and SBT allow modification of antimicrobial therapy. Gentamicin is useful in infections caused by Enterococci and nutritionally variant Streptococci. Fungal endocarditis requires anti-fungal drugs in combination. Preventionincludes patient education, oralhygiene, prevention of nosocomial infections, prophylaxis for IE not cost effective. Latest AHAs recommendations to use antimicrobial prophylaxis for IE for dental procedures and invasive procedures are useful.*
Keywords:*Infective Endocarditis,Risk factor,Bacteremia, Prevention.*

I. Introduction.

Infective endocarditis (IE) is defined as an infection of the endocardial surface of the heart, which may involve one or more heart valves, the mural endocardium or septal defect. It has been estimated annual incidence of 3 to 9 cases per 100,000 persons in the industrialized countries with male predominance [1,2].There is an increased incidence of IE in persons 65 years and older, which probably because people in this age group have large number of risk factors for IE.Over one third of IE cases in the United States were healthcare associated [1].IE has been clinically divided into acute(ABE) and subacute(SBE).This classifies both the rate of progression and severity of disease [3].Frequently isolated bacterial pathogens include *Streptococci,Staphylococci,Enterococci,*and fastidious gram-negative coccobacilli and HACEK(*Haemophilis*species,*Acinetobacilli,Cardiobacteriumhominis,Ekinella*sps,and *Kingnellakingae*)bacteria. Common risk factors include rheumatic heart disease, artificial heart valves,intra-cardiac devices and history of infective endocarditis[1].Clinical manifestations of IE vary from patient to patient, Fever occurs in 97% of people, other symptoms include fatigue, shortness of breath, anorexia, headache myalgia, and joint pain. The role of electrocardiography (ECG) in recognizing IE is controversial. Non-specific changes in ECG are quite common in endocarditis and in some cases indicate a life threatening complications [4-6].Diagnosis mainly by revised Duke criteria,echocardiography,transthoracic echocardiography(TTE),and blood culture [7,8].Treatment of choice has been vancomycin and ceftriaxone IV infusion for two to six weeks[9].IE is associated with 18% in-hospital mortality[10].The paper reviews the recent advances in the risk factors, diagnosis, and treatment of infectiveendocarditis.

II. Risk Factors

Risk factors in IE are based off the premise that in a healthy individual, bacteremia is cleared quickly with no adverse consequences [1].However, if the heart valve is damaged, the bacteria might have attached themselves to the valve, resulting in infection.Additionally, in individuals the weakened immune systems, the concentration of bacteria in the blood can reach levels high enough to increase the probability that some will attach to valve. Risk factors include: [1].

   a)   Artificial heart valve
   b)   Intracardiac devices,such as Implantable cardioverter-defibrillator
   c)   Unrepaired cyanotic congenital heart valve
   d)   History of infective endocarditis
   e)   Chronic rheumatic heart disease, which is an autoimmune response to repeated *Streptococcus pyogenes*infection

    f)   Age related degenerative valvular lesions
    g)   Hemodialysis in patients with renal failure and
    h)   Coexisting conditions, especially ones that suppress immunity.Diabetes mellitus, alcohol abuse,HIV?AIDS,and intravenous drug use all fall in this category.

Other conditions that result in high number of bacteria entering into bloodstream include colorectal cancer (mostly *Stretococcusbovis*), serious urinary tract infections (mostly*enterococci)* and drug injection (*Staphylococcus aureus*).With a large number of bacteria; even a normal heart valve may become infected. More virulent organism, such as *Staphylococcus aureus* can cause infective endocarditis by infecting even a normal heart valve[11].Other factors that increase the risk of developing IE are low level of white blood cells, immunodeficiency or immunosuppression, malignancy, diabetesmellitus, and alcohol abuse[3].

Dental procedures
    In the past, bacteremia caused by dental procedures (in most cases *Streptococci viridians*, whichresidein oral cavity),such as cleaning and extraction of a tooth was thought to be more clinically significant than actually was. However, it is important that a dentist or a dental hygienist be told of any heart problems before commencing treatment. Antibiotics are administered to patients with certain heart conditions as a precaution, although this practice has changed in the US, with new American Heart Associated guidelines in 2007,and in UK as of March 2008 due to new NICE(National Institute for Health and Clinical Excellence) guidelines[12].Everyday tooth brushing and flossing will similarly cause bacteremia. Although there is little evidence to support antibiotic prophylaxis for dental treatment, thecurrent American Heart Association (AHA) guidelines are highly accepted by clinicians and patients[13,14].

III.   Pathogenesis
    Damaged valves and endocardium contribute to the development of infective endocarditis. Specially, the damaged part of a heart valve forms a local clota condition known as non-bacterial thrombotic endocarditis (NBTE). The platelet and fibrin deposits that form as part of the blood clotting process allow bacteria to take hold and form vegetation.The body has no direct methods of combating valvularvegetations because the valves do not have a dedicated blood supply. This combination of damaged valves, bacterial growth, and lack of strong immune response results in infective endocarditis [1].

Damage to the valves and endocardium can be caused by:[1].
1. Altered, turbulent blood flow.The areas that fibrose, clot or roughen as a result of this altered flow known as jet injection. Altered blood flow is more likely in high pressure areas, so ventricular septal defects or patent ductus arteriosus can create more susceptibility than arterial septal defects.
2. Catheters electrodes,and other intracardiac prosthetic devices.
3. Solid particles from repeated intravenous injections.
4. Chronic inflammation, examples include auto-immune mechanisms and degenerative valvular lesions.

Bacteremia
    Bacteremia allows the conversion of the sterile thrombus to a vegetation.Bacteremia rates are highest for events that traumatize the oral mucosa, especially the gingiva, and progressively decrease with procedures involving the genitourinary and the gastrointestinal tract.A further increased risk of bacteremia occurs in the presence of a diseased mucosal surface,especially an infected one[15].

Bacterial factors,andintact endothelium
    Bacterial adherence to the thrombus is crucial in order for infection to occur. Multiple factors that enhance adherence,including the ability to produce dextran,cause aggregation of the platelets,and bind to fibronectin,appear to be important for most gram positive organisms that commonly cause IE.Resistance to host defense mechanisms is also pivotal.The ability of many gram negative bacilli to cause IE is limited by compliment-mediated bactericidal activity of serum[16].*Staphylococcus aureus* is the most common gram-positive organism ABE able to infect intact vascular endothelium.The reason for this are incompletely understood[16].

IV.   Clinical Manifestations
Frequent manifestations of IE include:
- Fever occurs in 97% of people, malaise and endurance fatigue in 90% of people [17].
- A changing heart murmur,weight loss,and coughing occurs in 35% of people[17].
- Vascular phenomena: septic embolism(causing thrombohemobolic problems such as stroke or gangrene of fingers), Janewaylesions (painless hemorrhagic cutaneous lesions on the palms and soles),intracranial hemorrhage,splinter hemorrhage,kidney infarcts,and splenic infarct [18].

- Immunologic phenomena:Glomerulonephritis which allowsfor blood and albumin to enter the urine.Osler's nodes (painful subcutaneous lesions in the distal fingers),Roths's spots on the retina, positive rheumatoid factor. Other signs may include, nightsweats, rigors, anemia and spleen enlargement [3].

Fifty-five per cent to 75% of patients with IE of native valve have predisposing conditionincluding rheumatic heartdisease, congenital heart disease, mitral valve prolapse, degenerative heart disease, asymmetric septal hypertrophy, or intravenous (*IV*) drug abuse [19-21].Nosocomial endocarditis is healthcare associated endocarditis in which the infective organism is acquired during stay in a hospital and it is usually secondary to presence of intravenous catheters, total parenteral nutrition lines pacemakers, etc. [5]. Weiand associates reported a case of bacterial IE with supraventricular tachycardia(SVT) as the initial presentation of disease, which finally leaded to catastrophic outcome [22].

V.   Diagnosis

In general, the Duke criteria should be fulfilled in order to establish the diagnosis of endocarditis [23]. The blood test C reactive protein (CRP) and procalcitonin have not been found to be particularly useful in helping make or rule out the diagnosis [24]. The**transthoracic echocardiogram** has sensitivity and specificity of approximately 65% and 95% if the echo cardiographer believes is 'probable' or 'almost certain' evidence of endocarditis [8].

Revised Duke criteria

Established in 1994 by the Duke Endocarditis Service and revised in 2000, the Duke criteria are a collection of major and minor criteria used to establish a diagnosis of IE [23]. According to the Duke criteria, diagnosis of IE can be definitive, possible, or rejected. A diagnosis of IE is **definite** if either of the following pathological or clinical criteria aremet: [1].

One of thesePathological criteria:
- Histology or culture of a cardiac vegetation, an embolizedvegetation, orintracardiac abscess from the heart finds microorganisms
- Active endocarditis

One of these Clinical criteria:
- 2 major clinical criteria
- One major and 3 minor criteria
- 5 minor criteria

Diagnosis of IE is **possible** if one of the following combinations of clinical criteria is met:
- One major and one minor criteria
- Three criteria are met

Major criteria
1. Positive blood culture with typical IEmicroorganisms, defined as one of the following: [1].
   Typical microorganisms consistent with IE from two separate blood cultures:
   Streptococcus viridians group,*Streptococcus bovis*,HACEK group,*Staphylococcusaureus*,community acquired *Enterococci.*
   Microorganisms consistent with IE from persistent blood cultures defined as:
   Two positive cultures of blood samples drawn > 12 hours apart or All of three or a majority of 4 separate cultures of blood(with first and last sample drawn 1 hour apart).*Coxiellaburnetti* detected at least one positive blood culture or IgG antibody titer for Q fever phase 1 antigen>1:800. This was previously a minor criterion.
2. Evidence of endocardial involvement with positive echocardiogram defines as:
   a. Oscillatingintracardiac mass on valve or supporting structures, in the path of regurgitantjets, or on implanted materials in the absence of an alternative anatomic explanation,or
   b. Abscess or
   c. New partial dehiscence of prosthetic valve or new valvularregurgitation (worsening or changing of preexisting murmur not sufficient).

Minor criteria
i) Predisposingfactor: known cardiac lesion,recreational drug injection,
ii) Fever > 38°C,
iii) Embolism evidence:arterial emboli,pulmonary infarcts,Janeway lesions,conjunctivar hemorrhage
iv) Immunological problems"glomerulonephritis,Osler's nodes,Roth's, Rheumatoid factor,

v) Microbiologic evidence:Positive blood culture (that doesn't meet a major criterion) or serologic evidence of infection with organism consistent with IE but not satisfying major criterion,

vi) Positive echocardiogram (that does not meet a major criterion) (this criterion has been removed from the modified Duke criteria).

Risk factor:Among people who do not use intravenous drugs and have a fever in the emergency room, there is less than 5 % chance of occult endocarditis.Mellors in 1987 found no cases of endocarditis nor of *Staphylococcal* bacteremia among 135 febrile patients in the emergency room [25].Weisse found that 13 % of 121 patients had endocarditis [7]. Marantz also found a prevalence of 13 % among such patients in the emergency room with fever[26].

VI. Treatment

High dose antibiotics are administered by the intravenous route to maximize diffusion of antibiotics molecules into the vegetation(s) from blood filling the chambers of the heart. This is necessary because neither the heart valves nor the vegetation adherent to them are supplied by blood vessels. Antibiotics are typically continued for two weeks depending on the characteristics of the infection and the causative micro-organism [9]. In acute endocarditis, due to the fulminant inflammation empirical antibiotics therapy is started immediately after the blood has been drawn for culture. This usually includes vancomycin and ceftriaxone IV infusion until microbial identification and susceptibility report with minimum inhibitory concentration(MIC) becomes available allowing for modification of the antimicrobial therapy to target the specific microorganisms. It should be noted that routine use of gentamicin to treat endocarditis has fallen out of favor due to lack of evidence to support its use (except in infections caused by *Enterococcus* and nutritionally variant *streptococci*) and high rate of complications [9].

Serum bactericidal titer (SBT) is the highest dilution of the patient's serum during antibiotic therapy that kills 99.9% of the standard inoculum of the patient's infecting organisms *in vitro*.Peak titers of 1:64 or 1;32 and trough titers of 1:32 obtained with a standardized SBT method correlate with bacteriologic cure. SBT is a poor predictor of bacteriologic failure. When using regimens considered optimal on the basis of clinical experience, monitoring therapy using SBT is not recommended [27].

The most common organism responsible for infective endocarditis is*Staphylococcus aureus*,which is resistant to penicillin in most cases. High rates of resistance to oxacillin are also seen, in which cases treatment with vancomycin is required [10].Viridans group *streptococcus* and *streptococcus bovis* are usually highly susceptible to penicillin and can be treated with penicillin of ceftriaxone[28].Resistant strains of viridans and *streptococcus bovis* are treated with penicillin or ceftriaxone along with a shorter 2 week course of an aminoglycoside during the initial stage treatment[28].Highly resistant strains of viridans group *streptococci*,nutritionally variants *streptococci* ,and *Enterococc*i are usually treated with a combination therapy consisting of penicillin and an aminoglycoside for the entire duration of 4-6 weeks[29].

Additionally, oxacillin susceptible *Staphylococcus aureus* native valve endocarditis of the right side can also be treated with a short 2 week course of beta lactam antibiotic like nafcillin with or without aminoglycoside.Surgical debridement of infected material and replacement of the valve with a mechanical or bio prosthetic artificial heart valve is necessary in certain situations [30]. **Fungal endocarditis** always requires a combined chemotherapeutic and surgical approach. Amphotericin B is administered at 0.5/kg/day. Most*Candida* and *Torulopsis* species are sensitive to fluocytosine,and 150 mg/kg/day may be added to the amphotericin however should not be used alone [31].

VII. Prevention and Recommendations

Prevention

Not all people with heart disease require antibiotics to prevent IE.Heart diseases have been classified into high, medium and low risk of development of IE.Those falling into high risk category require IE prophylaxis before endoscopies and urinary tract procedures. High risk diseases include:[32].

a) Prior endocarditis
b) Unrepaired cynanotic congenital heart diseases
c) Completely repaired congenital heart disease in their first 6 months
d) Prosthetic heart valves
e) Incompletely repaired congenital heart diseases
f) Cardiac transplant valvupathy

Antibiotics regimens recommended by the American Heart Association (AHA) for antibiotic prophylaxis: [12].

Oral Amoxicillin onehour beforeprocedure.Intravenous or intramuscular ampicillin one hour before the procedure.In patients allergic to penicillins-Azithromycin or clarithromycin orally one hour before the procedure.Cephalexin orally hour before the procedure or Clindamycin one hour before the procedure.

Current Recommendations[33].
1. Health care practioners and susceptible patients should be educated and informed regarding IE,with special emphasis on the importance of prompt diagnosis and treatment of IE.
2. Measures to maintain optimal oral and dental health should be emphasized in patients at risk for IE.
3. Interventions to prevent and promptly treat HAIs,(Health care associated Infections),especially CR-BSIs(Cather related blood stream infects),should be optimized.
4. Antibiotic prophylaxis for IE is an unproven practice that is not cost effective and that should no longer be regarded as standard of care.
5. Pending any new evidence, it seems reasonable to follow the AHAs latest recommendations to use antimicrobial prophylaxis for IE for dental procedures and for invasive procedures involving theskin, softtissues, respiratory tract, and urinary tract in the presence of active bacterial infection, but only for those relatively few patients at highest risk of an adverse outcome from IE[12].

VIII. Conclusion

Infective endocarditis (IE) is the infection of the endocardial surface of the heart, mainly caused by the *Streptococci* and *Staphylococc*i with 18% hospital mortality. American Heart Association (AHA) 2007 guidelines recommend antibiotic prophylaxis for the targeted patients.AHA guidelines are well accepted and practiced by the physicians and the dentists.

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