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Infective endocarditis- A systematic review with risk factors, etiopathogenesis and newer diagnostic and prophylaxis recommendations

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Abstract

Background: Infective endocarditis is an infection of mural endocardium and valves of heart. It is a relatively rare disease but significant because of its high inpatient and 1 year mortality rate of 20-25%. It leaves its mark with long lasting complications even in patients who get cured. It is more common in males than in females.

Methodology: Aim of this review was to develop a comprehensive analysis regarding all aspects of the disease, infective endocarditis. Various already published research articles available on public domain were analyzed as mentioned in references. No statistical test was used.

Results: Normal heart is resistant to infections but presence of predisposing conditions like mitral valve prolapse (MVP), rheumatic heart disease (RHD) and congenital heart defects can precipitate infection. High risk procedures like dental extractions, urinary catheterization and cardiac surgeries pave way for entry of microorganisms into blood which then stick to previously damaged endothelium of heart. Staphylococcus aureus is the most common causative agent in current time. Diagnosis of the disease is done by Duke's method, echocardiography which can be transthoracic echocardiography or transesophageal echocardiography, PCR, PET/CT scan. Newer methods like autoimmunohistochemistry and metagenomic analysis of DNA can be helpful for culture negative cases. Treatment is based on culture and sensitivity reports. Prophylaxis is now advised only to high-risk patients and not for routine use.

Conclusions: Infective endocarditis is a multisystem disease requiring extensive team of physicians involving cardiologists, surgeons, critical care and emergency management experts and allied professionals. Change in disease incidence to hospital acquired in recent times has made successful treatment more difficult. New synergistic antibiotic combinations and preventive models are developing areas of research. Several vaccinations against organisms causing IE are under research and provide for a ray of hope in future prevention strategies.

Keywords: Infective endocarditis; Rheumatic heart disease; Echocardiography; Staphylococcus aureus.

List of Abbreviations

IE- Infective Endocarditis
MVP- mitral valve prolapse
RHD- rheumatic heart disease
PCR- Polymerase chain reaction
PET/CT- Positron emission tomography/computed tomography
DNA- Deoxyribonucleic acid
HIV/AIDS- Human immunodeficiency virus
MRSA- methicillin resistant staphylococcus aureus
GI/GU- gastrointestinal/genitourinary
NBTE- nonbacterial thrombotic endocarditis
CFU- colony forming units
TTE- Transthoracic Echocardiography
TOE- Transoesophageal echocardiography

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PVE- prosthetic valve endocarditis
FDG-PET/CT- F-fluorodeoxyglucose positron emission/computed tomography
WBC/SPECT- white blood cell single-photon emission computed tomography
AST- Antimicrobial sensitivity testing
MSSA- methicillin sensitive staphylococcus aureus

Background

Infective endocarditis is a relatively rare disease but significant because of its high inpatient and 1 year mortality rate of 20-25%. It leaves its mark with long lasting complications even in patients who get cured. It was first described by French physician Lazare Rivière more than 350 years ago. William Osler at the end of the 19th century successfully elaborated the clinical manifestations of the infection on heart valves and mural endocardium. It is a multisystem disease with a myriad of complications and has shown considerable changes across time. The risk factors differ among developed and developing nations, incidence has been shifting from community acquired to hospital acquired IE and hence decrease in classical presentations is observed since the last decade. This has created a need for better diagnosing techniques and newer imaging methods. These methods have eased our catching of culture negative IE cases and an increase in the mean age of patients acquiring the disease is apparent. Better understanding of implicating organisms and evidence-based studies have helped in better preventive strategies and also opened up a prospect of vaccine development which is currently under study.

Methods

Aim of this review was to develop a comprehensive analysis regarding all aspects of the disease, infective endocarditis. Various already published research articles available on public domain were analyzed as mentioned in references. No statistical test was used.

Discussion

Epidemiology and demography: The incidence of Infective endocarditis varies across the globe, seen more so in developing countries because of rampant rheumatic heart disease, its principal risk factor. The incidence can also be different in different parts of the same country. Overall crude incidence according to various studies conducted mostly in developed countries ranges from 1.5 to 11.6 cases per 100,000 person-years [1]. The mortality rate however remains considerably uniform even after best interventions with in-hospital rate of 25% and a 5-year mortality rate of 45%. This owes to the complications of the disease with stroke seen in 15.8% ± 9.1% patients, intracardiac abscess leading to septic shock in 14.4% patients and heart failure, the most important complication in 32.4% patients. 32.4% ± 18.8% of patients will require valve surgery at some point during the disease course [2]. The mean age of patients acquiring the disease has also increased since the past few decades, from below 30 in 1920s to above 50 at present. This is because of the changing dynamics to heath case associated infection, better detection modalities and change in contemporary risk factors. Male to female ratio is 2:1. The most common implicating organism remains Staphylococcus aureus nevertheless.

Risk factors

1. Rheumatic heart disease- most common risk factor in developing countries. Involvement is valve is as follows- Mitral (41.4%)>Aortic (37.6%)>combined
2. Degenerative cardiac lesions (Mitral valve annular calcification) - most common risk factor in developed countries in patients with no previous valvular abnormality. It accounts for 30-40% of patients suffering from IE.
3. Mitral valve prolapse (MVP) - most common risk factor in developed countries, in patients with previous structural abnormality.
4. Cardiac devices- permanent pacemakers and cardioverter defibrillators
5. Prosthetic heart valve
6. Congenital cardiac defects like Bicuspid aortic valve, coarctation of aorta
7. IV drug abusers are at increased risk for tricuspid valve involvement
8. Procedures causing transient bacteremia- dental procedures [viridans streptococci],catheterisations, cardiac procedures, obstetric procedures
9. Impaired host defense mechanisms or immunocompromised states- cancer chemotherapy, organ transplantations, leukemia, HIV-AIDS, diabetes

Etiological agents: In recent times due to increasing incidence of healthcare-associated IE, there has been a corresponding increase in the prevalence of Staphylococcus aureus and coagulase-negative staphylococci and decrease in IE due to viridans-group streptococci. Enterococci are the third leading cause of IE linked to health care contact.

1. Staphylococcus aureus- Most common overall, seen especially in IV drug abusers and acute IE. Majority are methicillin resistant ie MRSA
2. Viridans streptococci- implicated in subacute IE
3. Staphylococcus epidermidis- implicated mostly in prosthetic valve IE
4. Enterococcus species – seen in older men with manipulation of GI/GU track
5. Pseudomonas species-in drug abusers

6. Culture negative endocarditis- Coxiella burnetti-most common cause (history of contact with livestalk), HACEK organisms- Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens and Kingella kingae , fungal species like candida and aspergillus, Bartonella species(history of contact with cats), Tropheryma whipplei (history of travel to tropics, causes afebrile form of IE), Brucella (history of consumption of unpasteurized milk and travel to Middle East)
7. Streptococcus bovis(gallolyticus)- IE associated with colon cancer

Pathogenesis

1. **Endothelial damage**: intact endothelium is resistant to infection and thrombus formation. It is because of this factor that IE more commonly developes on previously damaged valve or predisposing cardiac abnormalities as these conditions cause a turbulence to flow of blood across the valve. This in turn causes deposition of platelets on exposed subendothelial collagen through expression of VonWillebran factor (secreated by Wiebel-Palade bodies of endothelial cells), a condition called nonbacterial thrombotic endocarditis (NBTE).
2. Induction of Transient Bacteremia which is when bacteria temporarily enter bloodstream during manipulative dental or cardiac procedures and urinary catheterization. Experimental modules have shown bacteremia of 105–108 CFU per ml as significant. Routine tasks like brushing teeth etc do not produce bacteraemia in this range.
3. Colonization: The thrombus so formed serves as a site for adherence by organisms during periods of transient bacteraemia. The mechanism of adherence differs with each organism. Some organisms bind to components of NBTE like fibronectin, laminin or collagen while others bind directly to or are internalized by endothelial cells. For example-
• Adhesion of S. aureus is through S. aureus–specific surface proteins like clumping factor and coagulase that bind the fibronectin.
• Adherence of Viridans streptococci is by an extracellular bacterial derived polysaccharide called dextran.
• Other experimental adherence factors mediating streptococcal adhesion are-FimA(surface protein that acts as an adhesin in the oral cavity), the sialic acid-binding adhesin Hsa and a phage-encoded bacterial adhesin(mediates interaction between bacteria, fibrinogen and platelets of NBTE)
4. **Vegetation Formation**: the infecting organisms cause recruitment of inflammatory cells which initiate an inflammatory reaction inducing more fibrin and platelet deposition, in an attempt to trap the organism. The so formed friable mass of infecting organism forming complex biofilms embedded in fibrin-platelet meshworks and inflammatory cells is called a vegetation, which serves as the pathophysiologic hallmark of the disease. The vegetations of IE are generally large, irregular, and greyish present on the valve cusps and extending upto the chordae (as opposed to RHD where vegetations are small and along the line of closure of valve)
5. **Metastasis**: these bulky vegetations eventually break off and travel as mycotic emboli seeding into various organs of the body producing a multisystem disease and a wide array of clinical manifestations along with grim prognosis. This event furthermore inclines to sepsis and septic shock.
6. **Complications**: stroke (16.9%), embolization other than stroke (22.6%), heart failure (32.3%), and local intracardiac extension of infection (abscess (14.4%), fistula, pseudoaneurysm) may be seen.

Classification: Based on rapidity of evolution, virulence of organism and prognosis IE is divided into acute and subacute IE. Acute IE is presented on previously normal cardiac valves and has rapid evolution causing substantial morbidity and mortality even after proper antibiotic therapy. Valve replacement surgery is often required. Organisms implicated are of high virulence, most commonly hospital acquired S.aureus.
Subacute IE commonly affects damaged/deformed valves and progresses relatively gradually. Antibiotic therapy is often times curative. Causative organism is of low virulence able to bind to already damaged tissue like viridans streptococcus.

Clinical Manfestations: Considerable heterogeneity is exhibited in symptoms from one patient to another.
• Roth spots – retinal hemorrhages in eyes
• Splinter or subungual hemorrhages due to microthrombi
• Osler nodes – subcutaneous painful nodules in pulps of digits
• Janeway lesions – non-tender red lesions/rash on palms or soles
• Aching joints
• Pleuritic Chest pain
• Shortness of breath
• New regurgitate heart murmur
• Fatigue
• Hematuria
• Unexplained weight loss

Diagnosis: Classically detection was based on the combination of culture studies, clinical signs and symptoms and imaging results as given by the modified Duke's criteria. However, in the last decade there has been a shift from community acquired IE towards hospital acquired [4]. This has resulted in many patients presenting with few classic findings which prompted a shift towards newer diagnosing techniques with greater sensitivity. The duke's criteria is meant to a guide to "textbook" diagnosis and not as a replacement of all clinical suspicion. However, two things have remained the same for initial protocol upon suspicion-
• At least 3 sets of blood cultures should be obtained from different venipuncture sites, the first and last sample drawn at least 1 hour apart for organism identification and antimicrobial susceptibility testing.
• Echocardiography must be performed in all suspected patients.

Echocardiography: Transthoracic Echocardiography (TTE) shows growths (vegetations on the valve), abscesses, perforations, new regurgitations, stenosis (narrowing) or an artificial heart valve that has begun to pull away from the heart tissue suggesting infection - remains the mainstay imaging technique to identify endocardial lesions associated with IE [5].
Transoesophageal echocardiography (TOE) provides greater sensitivity for intracardiac vegetations (~95%), particularly when TTE is negative as in the cases of valvular or paravalvu-

lar complications and in prosthetic valve endocarditis (PVE). Three-dimensional TOE provides a more detailed image and useful in surgical planning.

Cardiac Computed Tomography: This investigation serves as a good adjunctive to TOE when a better depiction of valvular complications is needed or when echocardiography proves to be insufficient. Furthermore, cardiac CT is frequently used to preoperatively assess risks associated with surgical manipulation of vegetations.

Positron Emission Tomography/Computed Tomography (PET/CT)- F-fluorodeoxyglucose positron emission/computed tomography (FDG-PET/CT) and radiolabeled white blood cell single-photon emission CT/CT (WBC-SPECT/CT) have been specially implicated by the European Society of Cardiology in patients with suspected PVE for valves implanted for more than 3 months [5]. Its additional role in native valve IE remains controversial.

Polymerase chain reaction (PCR)- Using samples from explanted heart valves 16S ribosomal DNA for bacteria or 18S ribosomal DNA for fungi can be amplified and recovered to facilitate detection of etiological agent. Unfortunately, this method has shown low sensitivity towards detection of culture negative IE cases.

Some methods for detection of culture negative IE are-

Autoimmunohistochemistry: Uses a peroxidase-based method where patient's own serum acts as source of antibodies against specific pathogens to be detected in valve-tissue. Specific monoclonal or polyclonal antibodies detection against antigen. Metagenomic analysis of valvular DNA followed by 'next-generation' sequencing - to identify bacterial genome. Host gene signatures- aims at analysis of host inflammatory response unique for a pathogen or complication. For example- procalcitonin levels are significantly increased in the cases of endocarditis complicated with sepsis when compared to cases without sepsis.

However, these methods require more evidence-based research and clinical evaluation to explore their actual prospects.

Management: Because of a wide array of aetiologies, protection of bacteria by walled off vegetations and lack of concrete data from observational studies, there exists heterogeneity in treatment protocols. Treatment is thus based on AST reports and vancomycin is preferred by many as an empirical regimen.

For native valve infective endocarditis, treatment duration ranges from 2-6 weeks, whereas it is 6 weeks for prosthetic valve infective endocarditis. Right-sided vegetations tend to have lower bacterial densities and hence require shorter course.

In general, some common modalities of treatment are mentioned below. Note that these exhibit great variations based on specific strains, history of hypersensitivity in patient, patient demographic and geographical distribution.

1. Penicillin and ceftriaxone- useful against streptococci, enterococci, enterobacteriaceae , HACEK strains

Combination of penicillin/ceftriaxone with gentamicin has shown promising bacterical action and rapid clearance of organism.

2. Anti-staphylococcal antibiotics- nafcillin, cefazolin (for MSSA), vancomycin (for MRSA). Combination of daptomycin and fosfomycin has produced promising results in animal models of MRSA endocarditis since monotherapy is increasingly proving ineffective.

3. Anti-pseudomonal antibiotics- ticarcillin, piperacillin, tobramycin, ceftazidime, cefoperazone

4. Anti-fungal therapy- parenteral drugs like amphotericin or itraconazole with long them oral antifungal prophylaxis is recommended

Surgical treatment is needed is more than 50% patients. The most urgent indications for surgery are related to heart failure, persistence of refractory large(>10mm) vegetations, embolic complications and septic shock.

Prophylaxis: The previous conception of giving prophylactic treatment to all patients has been discarded after trails have shown similar outcomes both with and without therapy. American Heart Association guidelines state prophylaxis is no longer recommended for gastrointestinal or genitourinary procedures. Antibiotic prophylaxis is now limited to patients at high risk of IE undergoing dental procedures (cyanotic congenital heart disease, prosthetic heart valves, previous episode of IE) [6]. There is now increased emphasis on non-specific oral and cutaneous hygiene in patients undergoing health-care procedures.

Prospect of vaccinations- various vaccines are currently under research against common bacterial causes of IE. Vaccines against S.aureus are staphvax, v710 and SA4Ag. Recently, a multi-subunit vaccine targeting five known S. aureus virulence determinants — α-haemolysin (Hla), ess extracellular A (EsxA), ess extracellular B (EsxB), and surface proteins ferric hydroxamate uptake D2 and conserved staphylococcal antigen 1A — was described. When combined with a novel Toll-like receptor 7-dependent agonist, the five antigens provided high levels of Th1-mediated immunity against S. aureus in animal models [7]. Similarly, vaccine against candida albicans is under study.

Conclusions

Infective endocarditis is a complex, heterogeneous, evolving and multisystem disease requiring extensive team of physicians involving cardiologists, surgeons, critical care and emergency management experts and allied professionals. Because of heterogeneity in symptoms, prompt diagnosis and appropriate intravenous antibiotic therapy induction depends upon the clinical judgement and acumen of the physician. Change in disease incidence to hospital acquired in recent times has made successful treatment more difficult. New synergistic antibiotic combinations and preventive models are developing areas of research.

Declarations

Competing Interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

KG- Writing and conception of manuscript along with its substantive revisions and data collection. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission as well as agreed to be personally accountable for author's own contributions. The authors declare that all data were generated in-house and that no paper mill was used.

References

1. Cuervo G, Escrihuela-Vidal F, Gudiol C, Carratalà J. Current Challenges in the Management of Infective Endocarditis. Front Med (Lausanne). 2021; 8: 641243.
2. Marques A, Cruz I, Caldeira D, Alegria S, Gomes AC, Broa AL, João I, Pereira H. Risk Factors for In-Hospital Mortality in Infective Endocarditis. Arq Bras Cardiol. 2020; 114(1): 1-8.
3. Sullam PM, Drake TA, Sande MA. Pathogenesis of endocarditis. Am J Med. 1985; 78(6B): 110-5.
4. Kaye D. Changing pattern of infective endocarditis. Am J Med. 1985 Jun 28;78(6B):157-62.
5. Rajani R, Klein JL. Infective endocarditis: A contemporary update. Clin Med (Lond). 2020; 20(1): 31-35.
6. Hitzeroth J, Beckett N, Ntuli P. An approach to a patient with infective endocarditis. S Afr Med J. 2016; 106(2): 145-50.
7. Veloso TR, Mancini S, Giddey M, Vouillamoz J, Que YA, Moreillon P, Entenza JM. Vaccination against Staphylococcus aureus experimental endocarditis using recombinant Lactococcus lactis expressing ClfA or FnbpA. Vaccine. 2015; 33(30): 3512-7.