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International Journal of Pharmaceutical Research & Allied Sciences, 2020, 9(1):56-62

Research Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Infective Endocarditis Diagnosis and Management

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ABSTRACT

Background: *Infective endocarditis (IE) is a microbial (usually bacteria) infection affecting the heart tissue or the adjacent vascular endothelium. The blood-circulating microbes usually need to be available in a certain inoculum to allow invasion and thus infect the heart. Moreover, if the valve annulus is affected, the infection will spread into the extravascular areas. The main causative agents in IE are bacteria; however, other causes such as fungi are still a possibility in many cases. The most common bacteria seen are staphylococci and streptococci, and they collectively account for approximately 80% of cases; while S. Aureus, in particular is the most aggressive one.* ***Objectives:*** *We aimed to review the literature regarding the pathophysiology of infective endocarditis, clinical features, risk factors, diagnosis, and management of this disease.* ***Methodology:*** *PubMed database was used for articles selection.* ***Conclusion:*** *Diagnosing of infective endocarditis remains the pivotal step in management of these patients; thus, it had been studied widely for many years. Duke or modified Duke Criteria remain the most famous tool in diagnostic assessment, and they incorporate information from multiple sources into minor and major criteria which will reflect the probability of the disease in the suspected patients. The mainstay treatment of infective endocarditis is intravenous antibiotics, titred to serum levels, and the choice depends on the suspected causative organism and the valve involved in IE being native or prosthetic. Infective endocarditis prophylaxis is still a major point of difference among clinicians. Some institutions advocate for antibiotic prophylaxis in patients undergoing any dental procedure; while, others advised against prophylactic antibiotic.*

Key words: *Infective Endocarditis, Diagnosis, Management, Pathogens, Pathophysiology.*

INTRODUCTION

Infective endocarditis (IE) is a microbial (usually bacterial) infection affecting the heart tissue or the adjacent vascular endothelium. Even though infective endocarditis is a relatively rare disease compared to other major cardiovascular diseases, it has many life-threatening consequences, and everlasting complications in patients [1]. In developed countries, this disease has been shown to have an incidence that ranges from 1.5 cases and up to 20 cases per 100000 person annually [2, 3]. The high morbidity and mortality of this disease is noted with mortality rates reported as high as 25%, with some studies reporting one-third mortality rate in these patients [1, 4].

Evidently, only with early diagnosis and treatment, mortality and morbidity have been shown to be reduced, thus every clinician shall have fundamental knowledge about this fatal disease in order to provide the best care to their patient. Therefore, in this paper, we will review the proper literature discussing pathophysiology behind infective endocarditis, risk factors, diagnosis, and management options for such cases.

METHODOLOGY

PubMed database was used for articles selection using the following keywords: infective endocarditis, and its diagnosis and Management. With regard to the inclusion criteria, the articles were selected based on inclusion of one of the following topics: infective endocarditis evaluation, management and diagnosis. Exclusion criteria were all other articles which did not have one of these topics as their primary endpoint.

DISCUSSION

Infective endocarditis (IE) is a microbial infection that affects the cardiac tissue or the adjacent vascular endothelium. IE develops with the presence of a microbe, and the sum of many other factors that facilitate its invasion into the cardiac and/or surrounding tissues.

Pathophysiology

The blood-circulating microbes, usually need to be available in a certain inoculum to be able to invade and infect the heart eventually. The next step is adherence of these microbes to the tissues which is a pivotal step in infection. This step is easier if endocardial endothelium has damaged areas, and/or there is a foreign material exposed (in the bloodstream). This damage can be already there (old or chronic) or a result of a more acute cause. Common causes of this damage include valvular defects, ventricular septal defects (both will affect endocardium), patent ductus arteriosus (affecting endothelium), and/or exposure of prosthetic heart valves or pacemaker to bloodstream [5]. The next step after adhesion in the pathophysiology is the development of vegetations. These become the main source of embolization which eventually result in many complications. These vegetations form as a result of enzymes produced by the microbial organisms which disintegrate the surrounding tissues. Nevertheless, the most common cause of tissue injury is by turbulent blood flow from an acquired or congenital intracardiac abnormality. This explains the fact that the most common site of vegitations is on the closure sites, in the surface of the valves like, ventricular surface of semilunar valves, or the atrial surface of atrioventricular valves. The damage usually is infecting primarily the valve cusps and leaflets as well, resulting in “leakage points” of the affected valve. Moreover, if the valve annulus was affected, the infection will spread into the extravascular areas (invasive disease). Afterwards, a sterile thrombus is formed, by the deposition of fibrin and platelets, and this event can be with or without a direct trauma. Causative agents -mainly bacteria- tend to seed the thrombus, especially if the microbe has high adhesive capacity, virulence factors, and a relative concentration of the microbe needs to be in the bloodstream (e.g. bacteraemia). This will lead to a more “mature” thrombus with its core being fibrin, platelets and the causative microbial agent. There is no vasculature seen in this thrombus, thus the penetration of phagocytic cells (and resistance) are very rare and instead they will form a layer on the surface of the vegetation [5, 6]. Since IE can affect any of the four valves of the heart, and with various factors such as causative agent, type of the valve (prosthetic-mechanical or biological or native), and duration of infection; the pathophysiology can have huge differences among patients with various presentations and outcomes.

- **Immune System Role**

Another factor that is highly notable in the pathophysiology of this disease is the immune system and its response. Infective endocarditis stimulates both arms of immunity, cellular and humoral, with multiple effects clinically. The continuous bacteraemia noted in IE drive the production of many antibodies that circulate the blood. These antibodies include opsonic, agglutinating, antibodies directed against bacterial heat-shock proteins and macroglobulins. Antinuclear antibodies is noted as well and may contribute to the musculoskeletal symptoms, fever, and pleuritic pain [7]. Another example, is immune complexes found in almost all patients which can cause IE-associated glomerulonephritis. These complexes have been suggested as a probable cause to some peripheral manifestations such as Roth spots (retinal haemorrhages) and Osler’s nodes (a skin manifestation). Some of these antibodies has been studied heavily as options in treatment, and/or diagnosis and follow-up. For example, antibodies specific for the fibrinogen-binding protein clumping factor A (ClfA) resulted in a higher bacterial clearance when given with antibiotics in compared with only antibiotics [5, 8].

- **Causative Pathogens**

The main causative agents in IE are bacteria; however, other causes such as fungi are still a possibility in many cases. The most common bacteria seen are staphylococci and streptococci, collectively accounting for approximately 80% of cases. Moreover, Staphylococcus aureus is regarded as the most aggressive pathogen; however, healthcare-associated pathogens are proven to have destructive pathogens as well. Unfortunately, the prevalence of both S.aureus and health related pathogens are on the rise, with Enterococci now as the third leading cause of the disease. Other primarily health care-associated pathogens include gram-negative and fungal pathogens, and fortunately they are rare in occurrence [5]. Rarely, some obligatory intracellular pathogens such as Coxiella burnetii and Bartonella spp., may cause the disease. These pathogens have a special pathophysiology involving the absence of macrophage activation, and usually are not detected via the classical blood cultures. And even with all these agents, the blood culture do not always detect the pathogen (happens in 10% of cases), but new tests such as PCR can detect the causative agent in up to 60% of these "negative" cases. Some other causes that may show a negative blood culture include Brucella species, and Tropheryma whipplei [9]

Risk Factors

This disease has multiple risk factors that shall be assessed by every physician via good history taking and proper physical examination. These include age, hypersensitivity states, hormonal changes, high altitude immunocompromised patient (especially HIV patients), malignancy, uremia, any intravascular catheter, and IV drug usage (which damages mostly the tricuspid valve). However, the major key factor in this disease is structural heart damage, seen in for example congenital heart disease; however, rheumatic heart disease is the most frequent underlying factor, especially in the developing countries. As a result, the mitral valve is the most common involved site in infective endocarditis [10-12]. Presence of a prosthetic cardiac valve is another major risk factor, especially in the first year after implantation, and a higher risk is associated with mechanical valves compared to bio-prosthetic valves. Dental hygiene and/or recent dental operation are also important points to be asked in the history (associated with S. viridans infection). Some other risk factors that shall be focused on if the patient shows negative blood culture include contact with livestock, cats, homelessness, alcoholism, and extensive healthcare contact, especially if the patient has a prosthetic valve [5, 10].

Clinical Features

Infective endocarditis can present by its own signs and symptoms or by one of its complications. Thus, the clinician must have a respectable knowledge and good clinical suspicion threshold to diagnose IE. The most common symptoms in these patients are fever and chills. Moreover, other symptoms may include weight loss, malaise, anorexia, headache, night sweats, myalgia, joint pains, shortness of breath, cough, and/or chest pain (last three more common in IV drug users). IE can also present with signs of congestive heart failure (due to valvular insufficiency), and/or secondary (complications) symptoms such as focal-neurologic complaints (embolic stroke), and back pain (vertebral osteomyelitis). Healthcare-related or associated IE usually presents with elements of a sepsis syndrome like hypotension, leukocytosis, metabolic acidosis fever, and/or multiple organ failure. Some clinical classifications have been suggested for IE with acute and subacute infective endocarditis as its main components. Subacute IE has features of a more indolent and less severe disease, with up to 6 weeks of delay between the diagnosis and the actual onset of the disease. On the other hand, acute IE is a more aggressive disease, with acute and rapid onset of symptoms like high-grade fever, chills, and congestive heart failure [13]. Physical examination should be thorough, with special attention to the cardio examination, the clinician shall look for any invasive devices, signs of recent procedures, dentition status, and possible complications sites (especially embolic). Most common finding in heart examination is new-murmur which is seen in up to 85% of patients, but a changing murmur is noted only in 5 to 10%. However, if there were no significant findings in the physical examination to support the diagnosis, infective endocarditis cannot be ruled out, especially if the clinical suspicion is high [14].

In this disease, and due to multiple factors, the existing thrombus can be broken down to small masses that can travel along the bloodstream, and result in many complications. These emboli, if large enough can lodge and block fine blood vessels causing hypoxia and infarction to distal tissues. This is seen in embolic strokes, mycotic aneurysms, myocardial infarctions, and other body parts infarctions (kidney, spleen, mesentery, and even skin). This process is more common in patients with left-sided IE and seen in right sided IE if the patient has a patent foramen ovale. Overall, almost half of the patients will present with an embolic phenomena on clinical examination. Other complications can arise even from a not so large embolus, due to the fact that the bacteria is

embedded inside, which may create abscesses if a local tissue invasion happens. This is noted more in right-sided IE where pulmonary abscesses and empyema are frequent. In addition, extracardiac manifestations that can be seen in IE, can result from immune complex deposition and/or the constant bacteraemia state (by direct seeding of other tissues). Pathogen related toxins and enzymes may result in valve regurgitations (which is permanent even after therapy), para-valvular abscesses, fistulas, and even heart block [6, 15].

Diagnosis

Diagnosing of infective endocarditis remains the pivotal step in management of these patients, and thus it had been studied widely for many years. Duke or modified Duke Criteria remain the most famous tool in diagnostic assessment, and incorporate information from multiple sources into minor and major criteria. These criteria reflect the probability of the disease in any suspected patient. The criteria include history and physical examination findings mentioned earlier, echocardiography, microbiology, and even pathology results and/or findings (Table 1). Recently, new updates have been added to the criteria with some modifications to the approach of suspected cases. The updated approach starts first with transthoracic echocardiography (TTE) when IE is suspected by the clinician. Afterwards, if the results were uncertain, or even negative, but with a high clinical suspicion, transesophageal echocardiography (TOE) is done. Further imaging such as computed tomography (CT), positron emission tomography-computed tomography (PET-CT), and magnetic resonance imaging (MRI) are reserved for cases with difficulties in echocardiographic settings, and/or to detect distal (symptomatic or asymptomatic) embolization sites. Blood culturing is the appropriate first test, and at least three samples are taken with 1-hour interval between the first and last sample, preferably before antibiotics initiation, to avoid false negatives as much as possible. Other tests, such as agar culturing and mass spectrometry can be done to identify the infective agent. However, if the culture was negative (like we mentioned earlier), serological analyses by PCR is as considered the next step. If PCR was negative as well, anti-Pork antibodies, antinuclear, and antiphospholipid are to be performed afterwards. The lab shall always be notified with the probability of IE, and other tests like culturing of valvular tissue, urinalysis, and rheumatoid factor may further assist in diagnosis. Once the pathogen is recognized a susceptibility and sensitivity, testing must be performed to give the clinician the full picture of the pathogen and the best approach towards an effective treatment. New modalities of diagnoses are being incorporated in some IE cases, like molecular techniques to recover specific DNA and metagenome shotgun sequencing (WMGS). These tests can provide major breakthroughs in some cases, especially in the culture negative patients [16, 17].

Table 1: Modified Duke Criteria

Major Criteria	
Positive Blood Cultures for IE	Two separately positive blood cultures with classical organisms (S. virdians, S. aureus, HACEK group…)
	Persistently positive blood cultures over 12 hours apart OR all of three or four separate blood cultures, drawn 1 hour apart
	Single positive blood culture for Coxiella burnetii
Evidence of endocardial involvement	Positive echocardiogram
	Oscillating intra-cardiac mass / implanted material
	Abscess
	New partial dehiscence of prosthetic valve
	New valvular regurgitation
Minor Criteria	
Predisposing cardiac condition or IV drug use	
Fever equal to or more than 38 C	
Vascular phenomena e.g. emboli, septic infarcts etc.	

Immunologic phenomena e.g. glomerulonephritis
Note: Diagnosis is established with: 2 major criteria, or 1 major and 3 minor, or 5 minor criteria. Possible IE is considered with 1 major and 1 minor criteria or with 3 minor criteria.

Management

The mainstay treatment of infective endocarditis (IE) is intravenous antibiotics and the choice depends on the suspected causative organism and the valve involved in IE being native or prosthetic. Also, the antibiotic choice and its blood levels shall be optimized with the purpose of achieving bactericidal activity. The following discussion on antibiotic therapy in IE reflects the guidelines formulated by the European Society of Cardiology [18], American Heart Association [19] and the British Society for Antimicrobial Chemotherapy [20]. Starting with a native valve IE, the first thing to consider is the patient's clinical status. If clinically stable and does not show acute features of IE, empiric therapy is needless, and the choice of antibiotics should depend on blood cultures results. Otherwise, an empirical approach is needed in other cases such as instable patients and in cases with acute IE symptoms. The chosen antibiotic should cover staphylococci (including methicillin-resistant staph), streptococci, and enterococci. Thus, vancomycin (15-20 mg/kg/dose every 8-12 hours, not to exceed 2 g /dose) is a good initial therapy in most patients. The duration of therapy depends on the cultured pathogen and the severity of the disease. In general, treatment is given for six weeks starting form the first day after a blood culture is found negative. Shorter duration of therapy might be sufficient in mild cases secondary to non-resistant pathogens. Furthermore, in a study that included 74 patients with viridans streptococcal IE, none of the 66 patients who survived a four-week course of penicillin G relapsed and no patient was treated with this regimen died [21].

As for prosthetic valve IE, the main difference is the likelihood of complications and the need for surgical intervention is much higher. Thus, patients with prosthetic valve IE should be admitted in a hospital where cardiosurgical facility is available until they are afebrile. Also, a more intense antibiotic therapy should be administered with the same timing as in native valve IE. The antibiotic therapy of choice is a combination of nafcillin (or oxacillin), rifampin and gentamicin. The future of treatment in IE is focusing on pragmatism, like avoiding long term venous access in left-sided IE. And this is reflected in new studies trying to establish the effect and safety in replacing parts of IV antibiotic course with some oral antibiotics. This is made possible with the new antistaphylococcal antibiotics (dalbavancin and oritavancin) which showed high half-life (10-14 days), and may eventually be a replacement to the current IV treatment strategies [22]. Valve surgery is another option of therapy and is reserved in complicated cases with heart failure, uncontrolled infection, paravalvular complications (like abscess), and/or prevention of embolic events is needed. There are some relative indications for surgery that depend on the clinical judgment and the patient as a whole, and main example is vegetation of more than 10 mm in length [19].

Infective endocarditis prophylaxis is still a major point of difference among clinicians. While some institutions advocating for antibiotic prophylaxis in patients undergoing any dental procedure, others advised against prophylactic antibiotic as a whole. This can be attributed to the significant and severe lack of prospective studies and RCT studies done on this field [23]. Vaccine development has been suggested and been researched, with many candidates being discovered. However, the clinical testing and the effectiveness is still holding back the implementing of such breakthrough to the public usage [5].

Overall, infective endocarditis is a serious disease with many deadly complications and very complicated pathophysiology. The early diagnosis and treatment of this disease provide the best odds of survival in these patients. This paper discussed the recent protocols available and advised, and highlighted the relative points in pathophysiology that every clinician shall be familiar with.

CONCLUSION

Infective endocarditis is a complex fatal disease that had shown a great changing epidemiology, pathogens prevalence, and an ongoing rapid advances in both diagnosis and treatment. As a result, and to provide the optimal outcomes in the management, clinicians shall always have an updated understanding of all aspects, especially its rapid clinical (diagnostic and therapy) breakthroughs. Moreover, the approach to IE nowadays shall be done within a multidisciplinary team consisting of cardiologists, infectologists, imaging specialists, microbiologists and other specialties (e.g. neurologist). The horizons for further research are wide, especially in defining which patients can benefit the most from which diagnostic modality, the effect of newer treatment modalities, and the role of vaccines and prophylaxis.

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