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Literature review: Pathophysiology of endocarditis: Mechanism of infection and immune response

Ryan Nur Fikri, Muhammad Faruq Fajar and Fayi' Zayyan Mashyudi *

Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

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Abstract

Infective endocarditis (IE) is a severe and potentially fatal condition characterized by infection of the endocardial surface, particularly affecting cardiac valves. The disease arises from a multifactorial process involving endothelial injury, bacteremia, and host immune responses. Endothelial disruption promotes platelet-fibrin deposition, forming a sterile thrombus that facilitates microbial adhesion and colonization. Subsequent vegetation formation provides a protective microenvironment for pathogens, enabling persistence and resistance to host defenses and antimicrobial therapy. The immune response involves both innate and adaptive mechanisms, including activation of macrophages, neutrophils, and cytokine signaling pathways. However, dysregulated immune responses may contribute to tissue destruction and systemic complications such as embolization and immune complex deposition. Various factors, including host genetics, comorbidities, microbiota, and medical interventions, influence disease progression. A comprehensive understanding of the pathophysiology of endocarditis is essential to improve diagnostic strategies and therapeutic outcomes.

Keyword: Endocarditis; Infective Endocarditis; Pathophysiology; Immune Response; Vegetation; Immunothrombosis

1. Introduction

Endocarditis is defined as inflammation of the endocardial surface of the heart, most commonly caused by microbial infection known as infective endocarditis (IE) (1). This condition primarily affects cardiac valves and remains associated with high morbidity and mortality despite advances in antimicrobial therapy and diagnostic modalities (2).The pathogenesis of IE involves a complex interaction between circulating microorganisms, endothelial injury, and host immune responses (3). Clinical manifestations are often nonspecific, leading to delayed diagnosis and increased risk of complications such as systemic embolization, heart failure, and immune-mediated damage (4).Understanding the mechanisms underlying infection and immune response in endocarditis is essential to improve early detection, prevention strategies, and targeted therapeutic approaches (5).

2. Pathophysiology of endocarditis

The pathophysiology of infective endocarditis begins with endothelial injury, which may result from turbulent blood flow, valvular abnormalities, or intracardiac devices (6). This injury exposes the subendothelial matrix, promoting platelet adhesion and fibrin deposition, leading to the formation of non-bacterial thrombotic endocarditis (NBTE) (7). During episodes of transient or persistent bacteremia, microorganisms adhere to the thrombotic surface and proliferate, resulting in vegetation formation composed of bacteria, fibrin, platelets, and inflammatory cells (8). These vegetations serve as protective niches that limit immune cell penetration and reduce antibiotic effectiveness (9).

* Corresponding author: Fayi' Zayyan Mashyudi

Furthermore, vegetations can fragment and embolize, leading to systemic complications such as stroke, renal infarction, and splenic abscess (10). Progressive infection may also result in valvular destruction and cardiac dysfunction.

3. Mechanisms of infection in endocarditis

The mechanism of infection in infective endocarditis (IE) begins with endothelial injury, which represents the initial and critical step in disease development. Endothelial damage is commonly associated with abnormal hemodynamic stress, such as turbulent blood flow in valvular heart disease, congenital heart defects, or the presence of prosthetic valves and intracardiac devices (6). This injury disrupts the integrity of the endocardial surface and exposes the underlying extracellular matrix, triggering platelet adhesion and activation. Subsequently, fibrin deposition occurs, leading to the formation of sterile thrombi known as non-bacterial thrombotic endocarditis (NBTE), which provides a favorable surface for microbial colonization (7).

Following this, microorganisms gain access to the bloodstream through transient or persistent bacteremia originating from various sources, including dental procedures, skin infections, gastrointestinal or genitourinary manipulations, and invasive medical interventions (11). Circulating pathogens, particularly Staphylococcus aureus and Streptococcus species, possess specific surface proteins known as adhesins that enable them to bind effectively to damaged endothelium and exposed extracellular matrix components such as fibronectin and collagen (12). This adhesion process is crucial, especially under conditions of high shear stress within the cardiac chambers, as it allows bacteria to firmly attach and resist mechanical clearance by blood flow (13).

Once microbial adhesion is established, colonization begins with rapid bacterial proliferation and further recruitment of platelets and fibrin to the site of infection. This process results in the formation of mature vegetations, which are the hallmark pathological features of infective endocarditis (8). These vegetations consist of dense aggregates of microorganisms embedded within a matrix of fibrin and platelets, effectively creating a protective microenvironment. This structure limits the penetration of immune cells and reduces the efficacy of antimicrobial agents, thereby facilitating persistent infection and increasing the difficulty of treatment.

In addition to vegetation formation, bacteria within these structures often develop biofilms, which are highly organized communities of microorganisms encased in a self-produced extracellular polymeric substance (14). Biofilm formation significantly enhances bacterial survival by increasing resistance to antibiotics and evading host immune responses. This contributes to the chronicity of infection and is one of the main reasons for treatment failure and recurrence in infective endocarditis cases.

As the disease progresses, portions of the vegetations may become unstable and detach, leading to systemic dissemination through embolization. These embolic fragments can travel through the bloodstream and lodge in distant organs such as the brain, kidneys, spleen, and lungs (10). The resulting complications may include ischemic stroke, organ infarction, abscess formation, and septic emboli, all of which significantly contribute to the morbidity and mortality associated with infective endocarditis.

4. Immune response to endocarditis

The immune response in infective endocarditis (IE) involves a complex interplay between innate and adaptive immune mechanisms that aim to eliminate invading pathogens but may also contribute to tissue damage. The innate immune system represents the first line of defense and is activated through the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) expressed on immune cells (15). This recognition triggers rapid immune activation, leading to the recruitment of neutrophils and macrophages to the site of infection. These cells play essential roles in phagocytosis and pathogen clearance, while the complement system enhances bacterial opsonization and promotes microbial elimination (16). However, the effectiveness of innate immunity in IE is often limited due to the protective environment created by vegetations.

A distinctive feature of IE is the phenomenon of immunothrombosis, in which coagulation pathways are closely linked with immune responses to contain infection (17). Activation of the coagulation cascade leads to thrombin generation and fibrin deposition, which contribute to vegetation formation. In addition to its role in clot formation, thrombin also acts as a signaling molecule that amplifies inflammatory responses, thereby linking hemostasis and immunity. While immunothrombosis plays a protective role in restricting pathogen dissemination, excessive activation may contribute to pathological thrombosis and tissue injury.

The adaptive immune response is subsequently activated and involves both cellular and humoral components. T lymphocytes, particularly CD4+ T cells, enhance macrophage antimicrobial activity through cytokine secretion, thereby improving pathogen clearance (18). Meanwhile, B cells produce specific antibodies targeting circulating microorganisms, contributing to immune defense. Despite these mechanisms, the persistence of bacteria within biofilms significantly reduces the effectiveness of adaptive immune responses, allowing pathogens to evade immune detection and survive within the host.

Cytokine-mediated inflammation plays a central role in the pathophysiology of IE. Infection induces the release of pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which are essential for coordinating immune responses and controlling infection (19). However, excessive or dysregulated cytokine production may lead to systemic inflammatory responses, contributing to endothelial damage, tissue destruction, and clinical complications.

Over time, persistent infection and immune activation may result in immune-mediated complications. Circulating immune complexes formed between antigens and antibodies can deposit in various organs, particularly the kidneys, leading to conditions such as glomerulonephritis (20). In addition, immune-mediated vasculitis may develop, further exacerbating tissue injury and worsening clinical outcomes. These complications highlight the dual role of the immune system in IE, where protective mechanisms can paradoxically contribute to disease progression and organ damage.

5. Factors influencing the pathophysiology of endocarditis

The pathophysiology of infective endocarditis is influenced by a combination of host and microbial factors that determine susceptibility, disease progression, and clinical outcomes. One important aspect is host genetic variability, especially in regulating immune responses to infection. Genetic polymorphisms that affect cytokine production, pattern recognition receptors, and intracellular signaling pathways can influence how effective the host defense is (21). In some individuals, this may lead to a weaker immune response that allows pathogens to persist, while in others it can trigger an excessive inflammatory reaction that contributes to tissue damage.

Underlying cardiac conditions also play a significant role in the development of infective endocarditis. Structural abnormalities such as congenital heart defects, rheumatic heart disease, and degenerative valvular disorders can cause endothelial injury and abnormal blood flow (6,17). These conditions support the formation of non-bacterial thrombotic endocarditis, which then becomes a site for microbial adhesion and colonization. As a result, patients with pre-existing cardiac abnormalities have a higher risk of developing infective endocarditis.

Microbial virulence factors further determine the severity of the infection. Pathogens such as Staphylococcus aureus and Streptococcus species have several mechanisms, including adhesins, invasins, toxin production, and the ability to form biofilms (12,14). These features allow bacteria to attach to damaged endocardial surfaces, avoid immune responses, and persist within vegetations. Biofilm formation is particularly important because it increases resistance to antimicrobial therapy and contributes to persistent or recurrent infection.

Host immune status is another factor that influences disease progression. Conditions such as HIV infection, diabetes mellitus, malignancy, and the use of immunosuppressive therapy can weaken the immune system (22). This makes it more difficult for the body to control infection, so the disease may progress faster and lead to more complications with poorer clinical outcomes.

Furthermore, the widespread use of medical devices and healthcare interventions has significantly altered the epidemiology of infective endocarditis. Prosthetic heart valves, intravascular catheters, and implantable cardiac devices provide artificial surfaces that facilitate microbial adhesion and biofilm formation, thereby increasing the risk of infection (23). These device-related infections are often more difficult to treat due to the protective nature of biofilms and the potential need for surgical intervention.

Finally, alterations in the human microbiota, particularly in the oral and gastrointestinal environments, have been increasingly recognized as contributing factors in the development of infective endocarditis. Dysbiosis can increase the likelihood of transient bacteremia and influence systemic immune responses, thereby promoting microbial invasion and colonization of the endocardial surface (24). This highlights the importance of maintaining overall systemic and oral health in preventing the occurrence of IE.

6. Conclusion

Infective endocarditis is a complex disease resulting from the interaction between endothelial injury, microbial invasion, and host immune responses. The pathophysiological process begins with endothelial disruption, followed by platelet-fibrin deposition and formation of non-bacterial thrombotic endocarditis, which facilitates microbial adhesion and vegetation formation. These vegetations serve as protective environments for pathogens, enabling persistence, resistance to antimicrobial therapy, and increased risk of systemic embolization.

The host immune response plays a crucial role in controlling infection, involving both innate and adaptive mechanisms. Activation of neutrophils, macrophages, and complement pathways represents the initial defense, while T-cell and B-cell responses contribute to pathogen elimination. However, microbial evasion strategies such as biofilm formation and intracellular persistence limit immune effectiveness. Additionally, excessive inflammatory responses and cytokine release may contribute to tissue damage and immune-mediated complications, while immunothrombosis further links coagulation and inflammation in disease progression.

Several factors influence the development and severity of infective endocarditis, including host genetics, immune status, underlying cardiac conditions, and microbial virulence factors. Emerging evidence also highlights the role of microbiota in modulating immune responses and susceptibility to infection. Therefore, a comprehensive understanding of these mechanisms is essential to improve diagnostic accuracy, guide targeted therapy, and develop novel strategies aimed at reducing morbidity and mortality associated with this condition.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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