**LITERATURE REVIEW** **OPEN ACCESS**

# Molecular Pathophysiology of Infectious Esophagitis

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## 1. Introduction:

Esophagitis refers to inflammation of the esophageal mucosa, which can result from various factors, including infections caused by pathogenic microorganisms. Among the infectious agents implicated in esophagitis, *Helicobacter pylori*, *Candida albicans*, and Herpes Simplex Virus type 1 (HSV-1) are the primary pathogens with complex pathogenetic mechanisms. While esophagitis is often associated with gastroesophageal reflux disease (GERD) or other irritants, certain microbial infections can exacerbate or modify the disease course, intensify inflammation, and cause more severe tissue damage.

*Helicobacter pylori* (H. pylori), a Gram-negative bacterium typically colonizing the gastric mucosa, is well-established as a causative agent of gastritis and peptic ulcers. However, its association with esophagitis is frequently overlooked. Recent studies suggest that H. pylori infection can affect the esophagus both directly, through damage to the mucosal epithelium, and indirectly, by altering gastric acid secretion and gastric motility, thereby worsening gastroesophageal reflux conditions (1).

On the other hand, *Candida albicans*, an opportunistic pathogenic fungus, is often found in immunocompromised individuals, such as those with HIV/AIDS, diabetes mellitus, or undergoing immunosuppressive therapy. Esophageal infection by *Candida albicans* (Candida esophagitis) can lead to severe inflammation through mechanisms involving the transition from yeast to invasive hyphal forms and the secretion of hydrolytic enzymes that damage esophageal tissues. This morphogenetic transformation, coupled with biofilm formation, presents significant challenges in managing this infection (2). Additionally, Herpes Simplex Virus type 1 (HSV-1) is another infectious agent capable of causing esophagitis, particularly in immunocompromised individuals. Viral replication within the esophageal epithelium results in severe cytopathic damage, characterized by distinctive lesions observable during endoscopy. HSV-1 persists in the human body in a latent state and can reactivate repeatedly, leading to chronic and recurrent esophagitis (3).

A thorough understanding of the pathogenetic mechanisms underlying esophagitis caused by *H. pylori*, *C. albicans*, and HSV-1 is crucial for developing more effective diagnostic and therapeutic strategies. At the molecular level, the interaction between pathogen virulence factors and the host immune response plays a pivotal role in determining the success of infection and the extent of inflammation. Furthermore, persistent tissue damage can lead to serious complications, such as esophageal strictures and functional esophageal impairments (4,5).

Based on this background, this review aims to provide an in-depth understanding of esophagitis caused by infections with *H. pylori*, *C. albicans*, and HSV-1. It seeks to shed light on the pathogenetic mechanisms of these infections and the immunological factors that maintain a balance between infection clearance and avoidance of excessive inflammation. Additionally, the insights gained from this discussion could serve as a foundation for further research to develop more effective treatments for infectious esophagitis and enhance clinical practice, particularly in managing patients with digestive disorders associated with these microbial infections.

## 2. Main Body:

***Helicobacter pylori* (*H. pylori*)** is a spiral-shaped, Gram-negative bacterium primarily colonizing the gastric mucosa (5). Although its role in gastritis and peptic ulcer disease is well recognized, its association with esophagitis is less frequently discussed. This relationship manifests through both direct and indirect mechanisms, primarily involving alterations in gastric acid secretion often linked to *H. pylori*-induced gastritis (5,6). In the context of esophagitis, *H. pylori* can exacerbate gastroesophageal reflux disease (GERD) by increasing gastric acid secretion, particularly in infections localized to the antrum (7,8). This contrasts with corpus-predominant gastritis, which reduces acid secretion and paradoxically provides some protection against reflux esophagitis (9). Furthermore, *H. pylori*-induced inflammation can disrupt gastric motility, contributing to delayed gastric emptying and increased intragastric pressure, both of which promote reflux.

*H. pylori* also compromises the esophageal mucosal defense system. Direct mucosal damage arises from bacterial cytotoxins, particularly CagA and VacA, which weaken the epithelial barrier, enhance inflammation, and increase *H. pylori* pathogenicity. CagA is delivered into host epithelial cells via a type IV secretion system, where it undergoes phosphorylation and interacts with signaling pathways such as SHP-2 phosphatase and Wnt/β-catenin. These interactions disrupt tight junctions and epithelial integrity, rendering the esophageal lining more susceptible to acid-induced damage and inflammation (10).

VacA induces vacuolization in epithelial cells, modulates mitochondrial function, and triggers apoptosis. It also interferes with autophagy and perpetuates inflammation by inducing the release of pro-inflammatory cytokines such as interleukin-8 (IL-8). Together, CagA and VacA contribute to oxidative stress within the mucosa, promoting DNA damage and the release of reactive oxygen species (ROS) (10). Additionally, *H. pylori* lipopolysaccharides (LPS) interact with Toll-like receptor 4 (TLR4) on epithelial cells, activating nuclear factor-κB (NF-κB) and driving the transcription of pro-inflammatory genes (11). Adhesins like BabA and SabA facilitate adherence to gastric and esophageal mucosa, prolonging exposure to cytotoxins and exacerbating tissue damage (12).

The immune response to *H. pylori* is multifaceted, involving both innate and adaptive immunity. The innate immune response begins when *H. pylori* binds to pattern recognition receptors (PRRs), such as TLR4 and TLR2, on epithelial and immune cells. This interaction activates signaling pathways, including NF-κB, leading to the production of inflammatory mediators like IL-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α), which recruit neutrophils and monocytes to the infection site, contributing to acute inflammation (13,14).

The adaptive immune response is characterized by activation of T-helper (Th) cells, particularly Th1 and Th17 subsets. Th1 cells produce interferon-γ (IFN-γ), enhancing macrophage activity and fostering a pro-inflammatory environment. Th17 cells secrete IL-17, further recruiting neutrophils and amplifying the inflammatory response. However, regulatory T-cell (Treg) responses, which produce anti-inflammatory cytokines like IL-10 and transforming growth factor-β (TGF-β), are often insufficient to counteract this inflammation, leading to chronic esophageal injury. B cells contribute to the immune response by producing antibodies against *H. pylori* antigens. While these antibodies form part of the defense, their presence in the esophagus may

exacerbate inflammation via antibody-dependent cellular cytotoxicity (ADCC) (15).

Chronic immune activation in *H. pylori* infection fosters an oxidative stress environment and persistent epithelial damage, which, if unresolved, can lead to metaplasia or dysplasia of the esophageal mucosa (15). This underscores the importance of understanding and managing *H. pylori* infection to mitigate its contribution to esophagitis and related complications.

**Esophagitis caused by *Candida albicans*,** commonly referred to as Candida esophagitis, is most frequently observed in immunocompromised individuals, including those with HIV/AIDS, patients undergoing chemotherapy, or individuals receiving immunosuppressive therapy. It is also associated with conditions like diabetes mellitus and long-term corticosteroid use (16). The condition begins with *C. albicans* adhering to the esophageal epithelium via its surface adhesins, such as Als (agglutinin-like sequences) proteins and Hwp1 (hyphal wall protein 1), facilitating robust interactions with epithelial cells (17).

Following adhesion, *C. albicans* transitions from its yeast form to an invasive hyphal form. This morphogenesis is a critical virulence factor that enables the fungus to invade epithelial cells and compromise the mucosal barrier. The hyphal form secretes hydrolytic enzymes, such as secreted aspartyl proteinases (SAPs) and phospholipases, which degrade host epithelial components and enhance tissue invasion (17–19). The resulting damage leads to inflammation, ulceration, and clinical symptoms such as odynophagia, dysphagia, and retrosternal pain (17). The inflammatory response is characterized by neutrophil and macrophage infiltration into the esophageal tissue. These immune cells release cytokines and chemokines, contributing to the recruitment of additional immune effectors. However, excessive inflammation can exacerbate mucosal damage, intensifying the clinical manifestations (14).

The pathogenicity of *C. albicans* in esophagitis is driven by a combination of molecular mechanisms that facilitate adhesion, invasion, and immune evasion. A hallmark of *C. albicans* infection is its ability to transition from yeast to hyphal form, regulated by key signaling pathways such as the Ras-cAMP-PKA pathway and the MAPK pathway. Hyphal growth is associated with the expression of virulence factors such as SAPs and phospholipases (19). Transcription factors Efg1 and Cph1 play pivotal roles in regulating hypha-specific gene expression, ensuring the pathogen’s invasive capability (20).

Additional mechanisms include aspartyl proteinases and adhesin molecules. SAPs degrade host epithelial proteins, facilitating tissue penetration and immune evasion. SAP activity is tightly regulated and is crucial for mucosal infection development (19). Phospholipases disrupt host membranes, further enhancing fungal invasion. Adhesin molecules such as Als3 and Hwp1 are vital for early colonization of the esophageal epithelium. These molecules not only mediate attachment to host cells but also activate host signaling pathways that suppress local immune responses, promoting fungal persistence (17).

*C. albicans* is also capable of forming biofilms on mucosal surfaces and implanted medical devices, such as esophageal stents. Biofilms are highly resistant to antifungal therapy due to their structural complexity and alterations in fungal cell metabolism within the biofilm. Moreover, *C. albicans* employs various mechanisms to evade host immunity. For instance, it masks pathogen-associated molecular patterns (PAMPs) such as β-glucans in its cell wall, preventing recognition by pattern recognition receptors (PRRs) (20).

The immune response to *C. albicans* esophagitis involves a coordinated interaction between innate and adaptive immunity. Innate immunity serves as the first line of defense, recognizing fungal PAMPs via PRRs, such as Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) like Dectin-1. These receptors detect fungal cell wall components, including β-glucans, mannans, and chitin, activating signaling pathways like NF-κB and inducing the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (20). Neutrophils are the primary effector cells in controlling *C. albicans* infection. They utilize mechanisms such as phagocytosis, reactive oxygen species (ROS) generation, and the release of neutrophil extracellular traps (NETs) to kill fungal cells (14). However, *C. albicans*’ ability to transition into hyphal form and secrete hydrolytic enzymes enables it to resist phagocytosis and evade destruction.

Adaptive immunity plays a crucial role in long-term control of *C. albicans* infection. CD4+ T cells, particularly Th1 and Th17 subsets, are central to antifungal immunity. Th1 cells produce interferon-gamma (IFN-γ), which activates macrophages and enhances their fungicidal activity. Th17 cells secrete IL-17 and IL-22, recruiting neutrophils and strengthening epithelial barrier integrity (21). Humoral immunity, mediated by antibodies against fungal antigens, contributes to infection control by neutralizing fungal virulence factors and facilitating opsonophagocytosis. However, in the context of esophagitis, the role of antibodies is less well-defined compared to cell-mediated immunity (21).

In immunocompromised individuals, impaired neutrophil function or diminished T-cell-mediated immunity allows *C. albicans* to proliferate unchecked, leading to severe and recurrent esophagitis. For example, HIV/AIDS patients with low CD4+ T-cell counts are highly susceptible due to disrupted Th17-mediated responses. Persistent infection and the accompanying inflammatory response can result in chronic esophageal damage, fibrosis, and, in severe cases, stricture formation. Maintaining a balance between effective fungal clearance and limiting excessive inflammation is critical to preventing such complications (16).

**Herpes simplex virus type 1 (HSV-1)** esophagitis is most commonly observed in immunocompromised individuals, including those with HIV/AIDS, malignancies, or post-transplant conditions (8). The pathophysiology of this condition revolves around viral invasion, replication, and resultant cytopathic effects, which lead to inflammation and ulceration of the esophageal mucosa. HSV-1 enters epithelial cells via its envelope glycoproteins, including gB, gC, and gD, which bind host receptors such as heparan sulfate and nectin-1 (22). Once inside, the virus travels along sensory neurons, establishing latency in dorsal root ganglia. Reactivation, triggered by stress or immunosuppression, causes recurrent infection in the esophageal mucosa.

Tissue damage in HSV-1 esophagitis is primarily caused by the virus's cytopathic effects, which destroy infected epithelial cells. This damage produces vesicles that coalesce into characteristic ulcers, typically observed during endoscopy (23). Additionally, inflammatory mediators released during infection exacerbate mucosal injury, leading to symptoms such as odynophagia and dysphagia. HSV-1 further manipulates the immune system to evade detection, employing strategies such as downregulating major histocompatibility complex (MHC) molecules and inhibiting antigen presentation, facilitating persistent infection and recurrent esophagitis (14).

Complex interactions between viral factors regulate HSV-1 replication and its impact on host cellular mechanisms. Upon entry into host cells, the tegument protein VP16 activates transcription of genes encoding ICP0 and ICP4, regulatory proteins that prepare the host environment for viral replication. The early phase of viral gene expression follows, during which enzymes such as DNA polymerase, encoded by the UL54 gene, are synthesized to support viral DNA replication. The late phase involves the expression of structural proteins, such as capsids and glycoproteins, essential for virion assembly and release (24).

HSV-1 has profound effects on host cells. Viral-induced apoptosis in epithelial cells contributes to mucosal damage, although HSV-1 also inhibits apoptosis in neighboring cells to prolong infection. Viral proteins, such as ICP47, play a crucial role in immune evasion by blocking transporter-associated antigen processing (TAP), preventing MHC class I antigen presentation (25). Furthermore, HSV-1 disrupts host RNA and protein synthesis, effectively diverting cellular resources toward viral replication. Glycoproteins such as gC and gD are critical for initial host cell attachment and subsequent entry, while regulatory proteins like ICP0 suppress host antiviral factors and enhance viral gene expression (22).

Latency and reactivation are hallmarks of HSV-1 infection (26). During latency, the virus suppresses lytic gene expression and maintains its genome as an episome in sensory neurons. Reactivation is triggered by factors such as stress, immunosuppression, or environmental stimuli, leading to renewed viral replication and esophagitis (26). The immune response to HSV-1 esophagitis involves both innate and adaptive components, which aim to control infection but also contribute to inflammation and associated tissue damage. Innate immunity serves as the first line of defense, with pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) detecting viral components. For instance, TLR2 and TLR9 recognize viral DNA and glycoproteins, activating

downstream signaling pathways such as NF-κB, leading to the production of type I interferons (IFNs). These interferons induce the expression of antiviral genes that inhibit viral replication, although HSV-1 counteracts these effects using proteins such as ICP34.5. Natural killer (NK) cells also play a vital role by recognizing and eliminating infected cells during the early stages of infection (14).

Adaptive immunity is crucial for long-term control of HSV-1 infection. Cytotoxic CD8+ T cells recognize HSV-1 antigens presented by MHC class I molecules and eliminate infected cells via perforin and granzymes. CD4+ helper T cells enhance this response by producing cytokines such as IFN-γ, which boosts the antiviral activity of macrophages and other immune cells. Humoral immunity, mediated by B cells, generates antibodies against viral glycoproteins such as gB and gD, neutralizing extracellular virions and preventing further infection (14).

Despite robust immune mechanisms, HSV-1 employs several strategies to evade immune detection. The virus inhibits MHC class I and II expression, reducing T-cell recognition of infected cells. Viral glycoproteins, such as gE and gI, bind the Fc region of antibodies, disrupting antibody-mediated neutralization. Chronic infection and recurrent reactivation result in sustained immune activation, which can lead to tissue damage and scarring. Immunocompromised individuals often exhibit more severe disease due to diminished T-cell function and impaired interferon responses.

## 3. Conclusion

Esophagitis caused by Helicobacter pylori, Candida albicans, and Herpes Simplex Virus type 1 (HSV-1) involves complex pathophysiological mechanisms, where each pathogen disrupts the integrity of the esophageal mucosa through various virulence factors and interactions with the host immune system. H. pylori induces inflammation by affecting gastric acid secretion and epithelial damage through cytotoxins, while Candida albicans infects the esophagus via morphogenesis and enzymatic activity that damages tissue, forming biofilms that protect against therapeutic agents. HSV-1 contributes through viral replication that damages epithelial cells and immune evasion mechanisms, leading to recurrent infections and chronic inflammation. The immune response to these infections involves both innate and adaptive components, which may sometimes be insufficient to clear the infection in individuals with compromised immune function. A deeper understanding of these pathogenic mechanisms is crucial for more effective management of infectious esophagitis.

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