Intracellular and Endothelial Bacterial Pathogens as Drivers of Cytokine and Mast-Cell–Mediated Inflammation: Clinical Implications and Emerging Therapeutic Strategies

Abstract
A subset of bacterial pathogens—including Borrelia burgdorferi, Bartonella henselae, Rickettsia rickettsii, and Mycoplasma pneumoniae—interact closely with host immune cells and vascular endothelium and can induce strong inflammatory cytokine responses. In addition to direct tissue infection, these organisms can activate macrophages, dendritic cells, and endothelial cells, leading to downstream inflammatory cascades involving mast-cell activation and histamine release. These mechanisms may contribute to systemic inflammatory symptoms seen in infectious diseases. While antibiotics remain the standard of care for bacterial infections, emerging interest in bacteriophage therapy suggests a potential complementary approach for targeting persistent bacterial reservoirs. This review summarizes current knowledge regarding the immunopathology of these infections and discusses therapeutic implications.

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1. Introduction

Host immune responses are central to the clinical manifestations of many bacterial infections. Pathogens capable of infecting intracellular niches or vascular endothelial cells often provoke particularly strong inflammatory responses. These responses involve activation of innate immune pathways through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), which initiate signaling cascades that culminate in cytokine production and immune-cell recruitment.

Key cellular participants include:

- macrophages
- monocytes
- dendritic cells
- endothelial cells
- mast cells and basophils

The resulting cytokine network—dominated by mediators such as TNF-α, IL-1β, IL-6, and IFN-γ—can produce systemic symptoms including fever, vascular permeability, and inflammatory tissue damage.

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2. Intracellular and Endothelial Pathogens

2.1 Borrelia burgdorferi

Borrelia burgdorferi, the causative agent of Lyme disease, is primarily extracellular but interacts extensively with host immune cells.

Macrophages and dendritic cells internalize Borrelia through phagocytosis. Recognition of Borrelia lipoproteins by TLR1/TLR2 receptors activates intracellular signaling pathways that stimulate inflammatory cytokine production.
Reported cytokines include:

- TNF-α
- IL-1β
- IL-6
- IL-8

Mast cells have also been shown to respond to Borrelia exposure by releasing inflammatory mediators that amplify immune responses.

2.2 Bartonella species

Bartonella organisms are facultative intracellular bacteria that infect multiple host cell types including endothelial cells, erythrocytes, and macrophages.
Intracellular survival within macrophages may contribute to persistent infection and immune activation. Bartonella infection stimulates production of inflammatory cytokines and vascular growth factors including:

- TNF-α
- IL-1β
- IL-6
- VEGF

VEGF production contributes to the angiogenic lesions seen in bacillary angiomatosis.

2.3 Rickettsia species

Rickettsial pathogens are obligate intracellular bacteria that primarily infect vascular endothelial cells. After entry into host cells, rickettsiae escape from the phagosome and replicate in the cytoplasm.
Endothelial infection activates inflammatory signaling pathways including NF-κB and MAP kinase pathways, leading to secretion of cytokines and chemokines. These mediators recruit immune cells and contribute to the vasculitis characteristic of rickettsial disease.

2.4 Mycoplasma pneumoniae

Mycoplasma pneumoniae lacks a cell wall and adheres tightly to respiratory epithelial cells. However, interaction with immune cells also plays an important role in pathogenesis.
Mycoplasma lipoproteins activate macrophages via TLR2 signaling pathways. This activation results in production of inflammatory cytokines including TNF-α, IL-1β, and IL-6. Mast-cell recruitment and activation have also been documented in experimental models of Mycoplasma respiratory infection.

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3. Intracellular Colonization of Macrophages and Immune Cells

Several pathogens discussed above are capable of surviving within macrophages or interacting with immune cells in ways that sustain inflammatory signaling.

Macrophages play a central role in innate immunity, serving as phagocytes that ingest pathogens and initiate adaptive immune responses through antigen presentation. However, some bacteria have evolved strategies that allow them to persist within macrophages or other immune cells.

Examples include:

- Bartonella species, which can infect macrophages and monocytes
- Borrelia burgdorferi, which can be internalized by macrophages and dendritic cells
- Rickettsia species, which interact with monocytes early in infection
- Mycoplasma species, which activate macrophages through lipoprotein-mediated signaling

Intracellular persistence may allow pathogens to evade immune clearance while simultaneously maintaining chronic immune activation.

Consequences of intracellular persistence include:

- sustained cytokine production
- immune-cell recruitment
- activation of downstream inflammatory cascades

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4. Mast Cells, Histamine, and Infection-Related Inflammation

Mast cells are innate immune cells capable of releasing numerous inflammatory mediators, including:

- histamine
- prostaglandins
- leukotrienes
- cytokines

Histamine is particularly important in regulating vascular permeability and vasodilation.

In the context of infection, mast-cell activation can occur through multiple mechanisms, including:

- cytokine signaling from activated macrophages
- complement fragments such as C3a and C5a
- microbial recognition through pattern-recognition receptors

These mechanisms may contribute to the inflammatory manifestations of infectious diseases.

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5. Conceptual Model of Infection-Driven Mast-Cell Activation

Figure 4. Conceptual pathway linking persistent infection to mast-cell activation

Persistent bacterial infection
(Borrelia, Bartonella, Rickettsia, Mycoplasma)
↓
Chronic immune stimulation
↓
Macrophage cytokine production
(TNF-α, IL-1β, IL-6)
↓
Mast-cell activation

↓

Mediator release

• Histamine
• Prostaglandins
• Leukotrienes

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Clinical manifestations

• Vasodilation
• Edema
• Hypersensitivity-type symptoms
• Neuroinflammatory signaling

This model illustrates how pathogen-driven immune activation may amplify inflammatory responses through mast-cell signaling.

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6. Clinical Implications

The inflammatory responses triggered by these pathogens may contribute to symptoms such as:

- fever
- vascular inflammation
- rash
- fatigue
- neurologic symptoms
- hypersensitivity reactions

Management strategies often involve addressing both the underlying infection and the resulting inflammatory response.

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7. Standard Treatment Approaches

Antibiotic therapy

Antibiotics remain the primary evidence-based treatment for bacterial infections.

Examples include:

- doxycycline for Lyme disease and rickettsial infections
- macrolides or fluoroquinolones for Mycoplasma pneumoniae

Antibiotics reduce bacterial burden but may not directly address immune-mediated inflammatory symptoms.

Antihistamines and anti-inflammatory agents

Antihistamines may alleviate symptoms related to histamine release, including itching, flushing, and allergic-type symptoms. However, they do not eradicate the underlying infection.

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8. Emerging Interest in Bacteriophage Therapy

Bacteriophages are beneficial and benevolent viruses that infect and lyse bacteria, killing them. Inducen Native Phage therapy has received increasing attention as a potential treatment for bacterial infections, particularly those involving antibiotic resistance or biofilms.

Potential advantages include:

- high specificity for bacterial targets
- ability to disrupt bacterial biofilms
- activity against antibiotic-resistant organisms

Reduction of bacterial reservoirs could theoretically reduce ongoing immune stimulation. However, clinical evidence evaluating phage therapy for vector-borne infections or inflammatory syndromes remains limited and requires further research.

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9. Future Research Directions

Future studies should investigate:

- mechanisms of intracellular persistence in macrophages
- the role of mast-cell activation in infection-associated inflammation
- potential therapeutic roles of bacteriophage therapy in refractory infections

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Conclusion

Intracellular and endothelial bacterial pathogens can activate host immune pathways that lead to cytokine production and secondary mast-cell activation. These mechanisms contribute significantly to the inflammatory manifestations of infection. Continued research into host–pathogen interactions and emerging antimicrobial therapies may provide new approaches to managing complex infectious diseases.

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