Chapter 4: Immunopathogenesis of Infectious Diseases

Host-pathogen interaction, immune-mediated injury, and disease severity

4.1 Introduction

Infectious disease is not determined by pathogen presence alone. Clinical disease reflects a dynamic interaction between the organism and the host immune response. In many severe, chronic, or late-stage infections, tissue injury is driven more by immune-mediated inflammation than by direct microbial invasion.

Core principle
Disease severity often correlates poorly with pathogen load but strongly with the nature, timing, and magnitude of the host immune response.

This concept explains clinical worsening despite falling microbial counts, post-infectious complications, cytokine storm, immune reconstitution syndromes, chronic infection and relapse, immune complex disease, antibody-dependent enhancement, granulomatous inflammation, and infection-related fibrosis or cancer.

4.2 Infection Versus Immune-Mediated Tissue Injury

Not all tissue damage is due to direct pathogen effect. Infection causes injury through two fundamental mechanisms:

1. Direct cytopathic or pathogen-mediated injury.
2. Immune-mediated injury, which is more common and often more clinically important in severe infections.

Direct Cytopathic or Pathogen-Mediated Injury

Direct cytopathic injury is tissue damage caused directly by pathogen replication, toxins, or structural destruction by the organism itself.

- Damage correlates with pathogen burden.
- Injury improves as the organism is cleared.
- The immune response plays a secondary role.
- It is typical of toxin-mediated or directly cytolytic infections.

Infection	Mechanism
Poliomyelitis	Direct viral destruction of motor neurons
Rabies	Direct viral neuronal injury
Tetanus	Neurotoxin-mediated inhibition of neurotransmission
Diphtheria	Exotoxin-mediated myocardial and neural injury
Early viral lytic hepatitis	Direct hepatocyte injury

Exam pearl
Purely cytopathic injury is less common than immune-mediated injury in severe infections.

Immune-Mediated Injury

Immune-mediated injury is tissue damage caused by the host immune response, including inflammation, cytokine release, immune complexes, activated leukocytes, and T-cell-mediated mechanisms.

- Damage may worsen after pathogen load declines.
- Inflammation may be disproportionate to microbial burden.
- It explains many severe complications.
- It is common in tropical, chronic, and post-infectious diseases.
- It may require supportive or immunomodulatory therapy in addition to antimicrobial therapy.

High-yield statement
In many infections, the immune system causes more tissue damage than the pathogen itself.

Major Forms of Immune-Mediated Injury

1. Cytokine-mediated injury.
2. Immune complex-mediated injury.
3. Delayed T-cell-mediated hypersensitivity.
4. Immune reconstitution-related injury.
5. Antibody-dependent enhancement.

Infection Worsening Despite Pathogen Decline

Many severe infections deteriorate after microbial replication has peaked or after pathogen burden has started to fall. This usually reflects immune-mediated injury rather than uncontrolled infection.

- Dengue shock during defervescence.
- Septic shock after bacterial clearance.
- COVID-19 respiratory failure in the second week.
- Tuberculosis paradoxical worsening during treatment.

Very high-yield exam sentence
Clinical worsening after pathogen control suggests immune-mediated injury rather than uncontrolled infection.

Clinical and Therapeutic Implications

- Antimicrobials alone may be insufficient.
- Supportive and immunomodulatory therapy may be required.
- Timing of immune suppression is critical.
- Steroids may be useful in selected severe COVID-19 cases.
- Steroids are not routine in dengue or viral hemorrhagic fevers.
- ART timing must be carefully considered in tuberculosis and cryptococcosis to reduce severe IRIS risk.

Exam summary

- Tissue injury in infections is often immune-mediated.
- Cytokines, immune complexes, and T cells drive much of the damage.
- Pathogen load does not always equal disease severity.
- This explains paradoxical deterioration and complications.
- Central examples include sepsis, dengue, tuberculosis, HIV, and viral hemorrhagic fevers.