Pathophysiology — Plasma Leakage

DENV-infected cells release inflammatory mediators, immune complexes are formed, and the complement cascade is activated resulting in increased vascular permeability and hemorrhagic manifestations that characterize severe dengue.

- Memory T lymphocytes that recognize DENV become activated and secrete cytokines adding to the tissue inflammation during secondary infections. Clinically significant plasma leakage is defined by WHO as plasma leakage leading to shock or fluid accumulation, sufficient to cause respiratory distress, or both.

Clinically evident plasma leakage becomes apparent near the time of defervescence and lasts about 24–48 hours.

- Leakage occurs primarily into the pleural, peritoneal and pericardial cavities. Typically, patients have no generalized edema unless given too much intravenous fluid.

Mechanisms are not completely understood, but there is evidence that reactive oxygen species, enzymes, and pro-inflammatory molecules (for example, TNF-α, IL-6, IL-8 and IFN-γ) break down the endothelial glycocalyx layer, allowing plasma to reach the underlying intercellular junctions and leak out of the blood vessel.

- Under normal circumstances, the endothelial glycocalyx acts to restrict the movement of negatively charged or large molecules within plasma so that they cannot leak from the blood vessel.

- Patients with dengue often have hypoalbuminemia and proteinuria because albumin and other smaller plasma proteins leak from blood vessels.

- DENV and DENV non-structural protein-1 can adhere to heparan sulfate, a key structural element of the glycocalyx. Increased urinary heparan sulfate excretion has been detected in children with severe infection.

- Changes to the glycocalyx are transient; leakage resolves spontaneously.

- DENV is not known to infect endothelial cells. Only minor, nonspecific changes have been detected in histopathological studies of the microvasculature. No tissue inflammation, cellular death, or damage is evident.