Infection and Venous Thrombosis: Experimental Insights

Peter K. Henke MD
Jobst Vascular Laboratories, University of Michigan

No Disclosures

1.8 million medical patients
15,000 VTE

Infection and Thrombosis

10,344 post-surgical patients
22 VTE risk factors


Could sepsis lead to “priming” of the endothelium?

Hypothesis

Sepsis Dysfunctional vein wall Thrombosis cellular adhesion molecules

Phase I

Effect of endotoxemia on vein wall

ELISA - vein wall cellular adhesion molecules (CAMs)

Intravital microscopy for leukocyte trafficking

Phase I

SAINE [vehicle] LPS (20ng/kg)

2hr

Harvest
LPS upregulates vein wall CAMs

LPS increases leukocyte trafficking

Phase II

Phase II Effect of endotoxemia on thrombosis
Thrombus weight and CAMs

LPS treated mice form larger thrombi

Phase III

Phase III Effect of inhibitors on endotoxemia induced thrombosis
CAM inhibition
In a mouse model of endotoxemia:
- CAMs are upregulated and leukocyte trafficking occurs locally in the vein wall.
- Results in increased thrombotic potential, which can be mitigated with ICAM inhibition.

- ICAM may be central to sepsis related DVT.
- Translation: ICAM inhibition may represent a unique strategy to prevent sepsis related DVT.

How about Gram Negative Pneumonia?

A multi-disciplinary approach
- Klebsiella pneumonia
- Deep Vein Thrombosis Model

Pneumonia and CAMs
- Post-thrombosis, mice treated with klebsiella have increased circulating VCAM-1, ICAM-1, E selectin and P selectin.
Pneumonia and Thrombosis

- Mice treated with Klebsiella have increased H3 and cathepsin G (NETs/PMN markers) in thrombus compared to controls.

Pneumonia and Neutrophils

- Natural history of Klebsiella pna in mouse: circulating CAMs increase as mice get sicker.
- Klebsiella treated mice have larger thrombi.
  - Associated with increased circulating and vein wall CAMs
  - Associated with increased PMN/NETS markers in the thrombus

- Translation:
  - High level of VTE prophylaxis for pneumonia/sepsis patients currently
  - Novel non-anticoagulant agents such as anti-CAMs to prophylax against VTE in pneumonia patients

Pneumonia and Thrombosis: Summary