CARDIOLOGY 2025

Inflammatory Response and CPB – Developments and Understanding

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Feb 20, 2025

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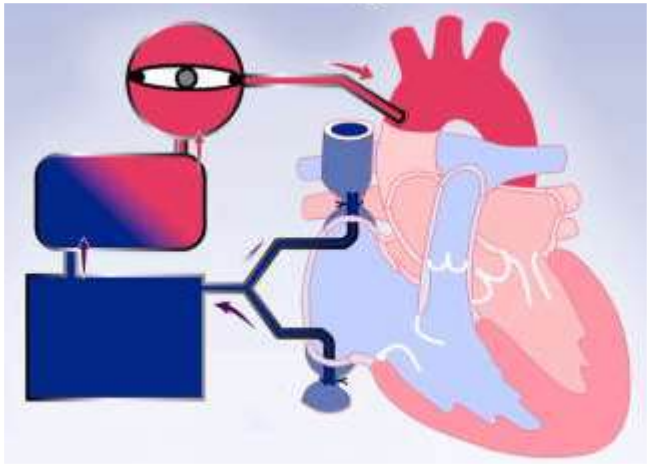
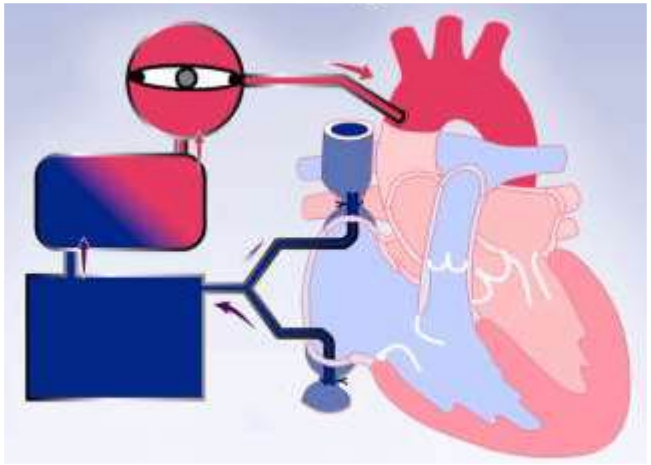
Financial Disclosures

None

CARDIOPULMONARY BYPASS

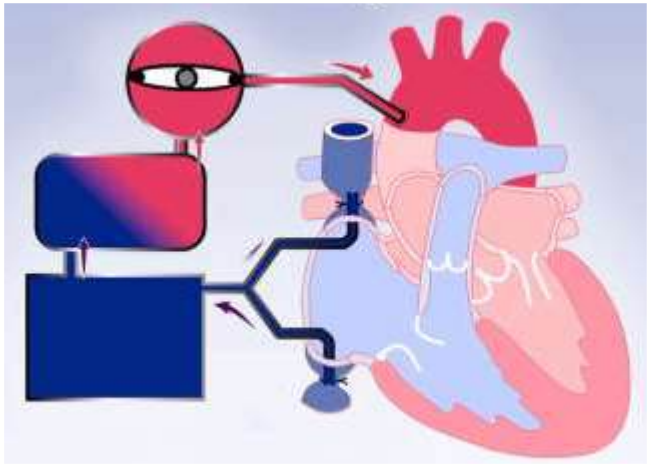


CARDIOPULMONARY BYPASS -- PATHOPHYSIOLOGY



- Synthetic surfaces
- Shear stress
- Ischemia-reperfusion injury
- Pulsatile flow converted to laminar flow
- Blood product administration
- Heparin and protamine administration
- Hypothermia

CARDIOPULMONARY BYPASS -- PATHOPHYSIOLOGY



- Synthetic surfaces
- Shear stress
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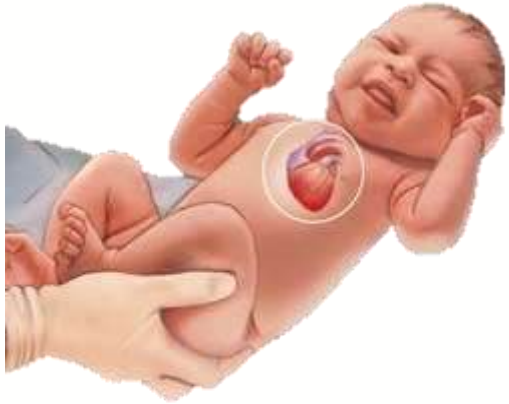
- Hypothermia

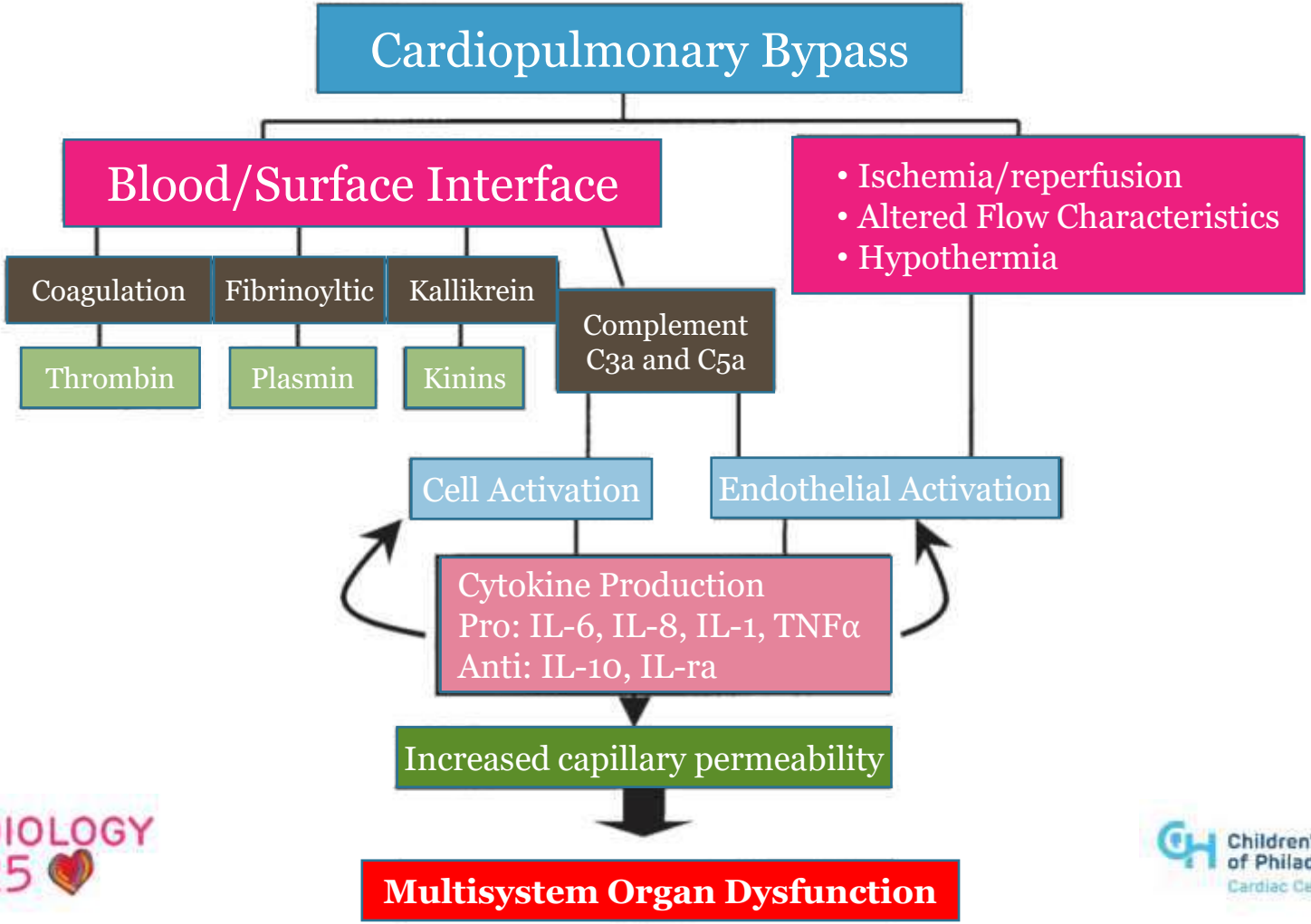
→ Systemic inflammation and multiorgan dysfunction

PEDIATRIC PATIENTS AT INCREASED RISK

- Immature organ systems → increase susceptibility to injury
- Higher metabolic demands → Higher pump flower rates
- CPB circuit to patient size ratio → Greater exposure of blood to foreign surface of bypass circuit



Kozik and Tweddel, 2006



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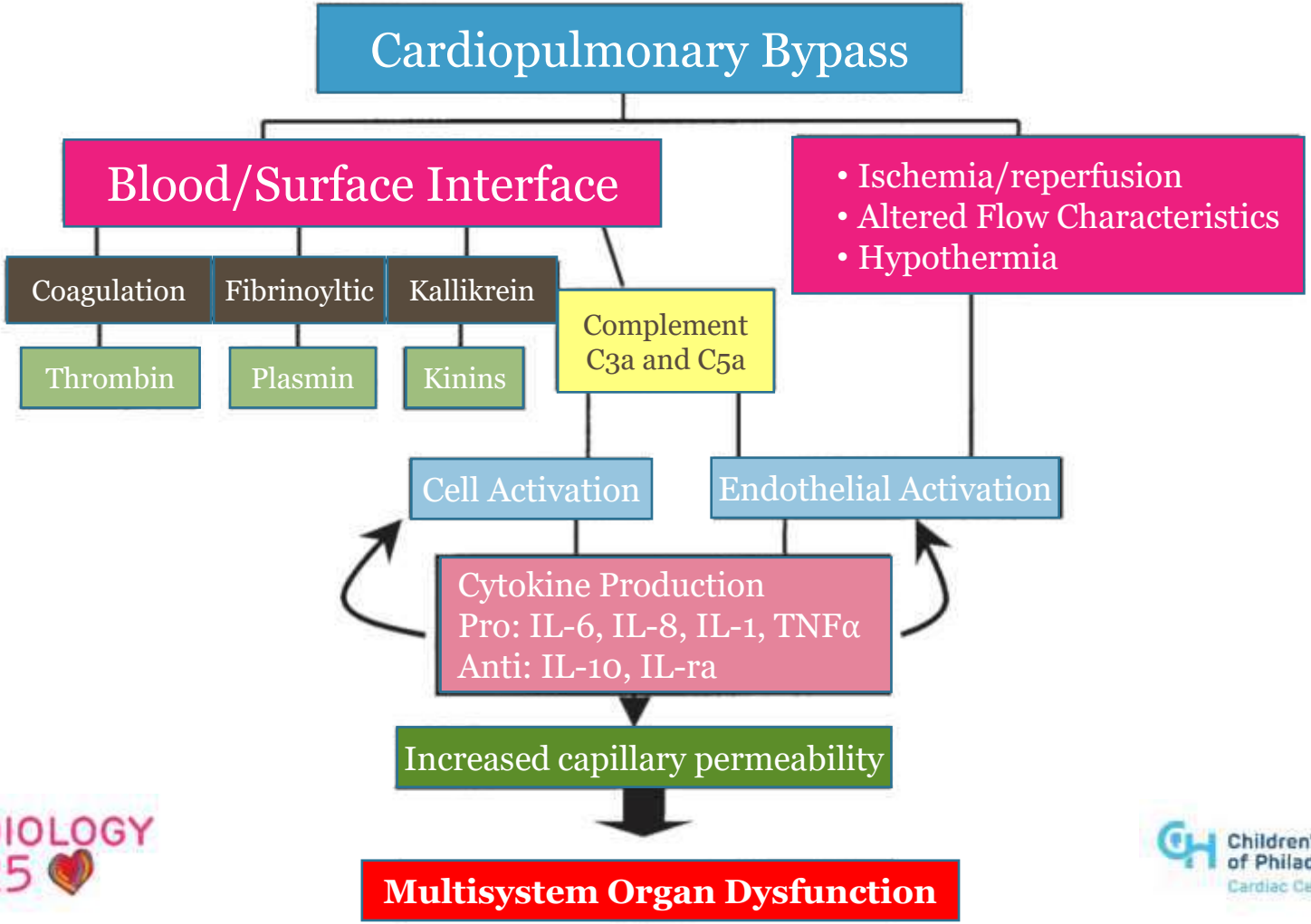

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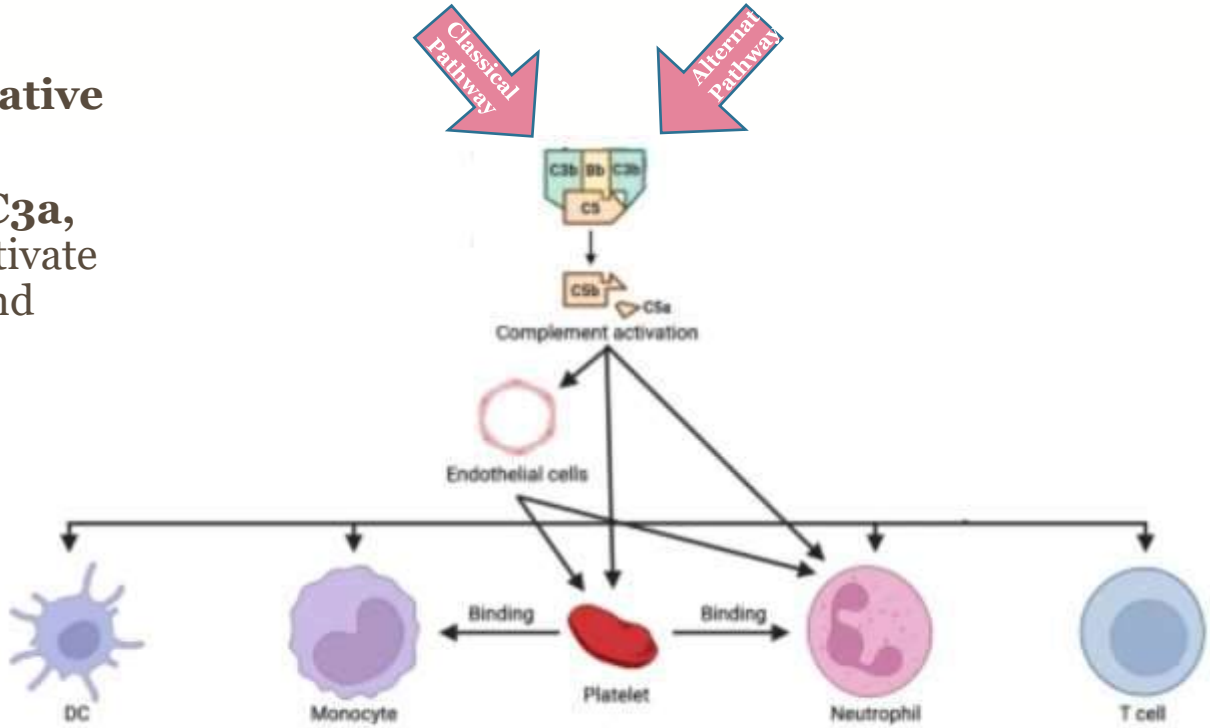
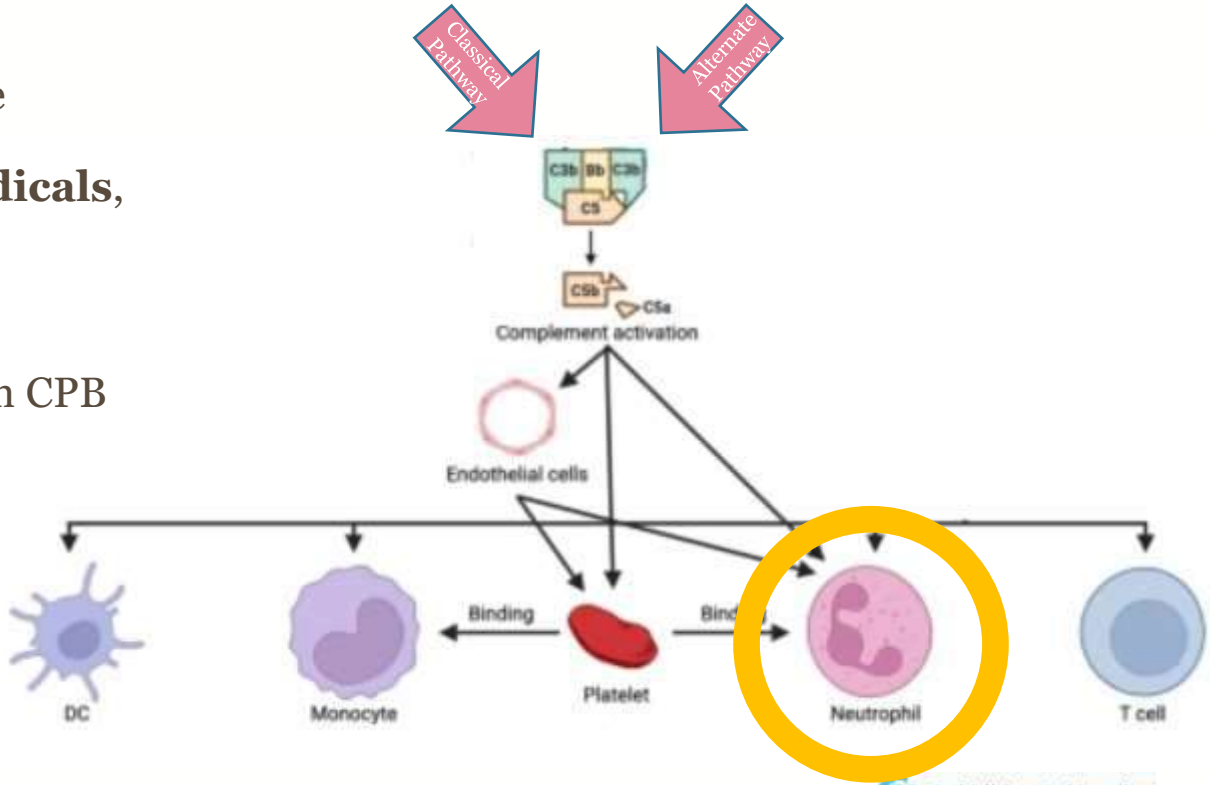
COMPLEMENT ACTIVATION

- CPB triggers both **alternative** and **classical** pathways.
- Leads to **formation of C3a, C4a, and C5a**, which activate neutrophils, basophils, and mast cells, releasing inflammatory mediators.
- Some studies suggest **correlation with complications**, though findings are inconsistent.



NEUTROPHIL ACTIVATION

- Neutrophils adhere to the endothelium, **release proteases and free radicals**, causing **capillary leak syndrome**.
- More **pronounced in children**, correlated with CPB duration..



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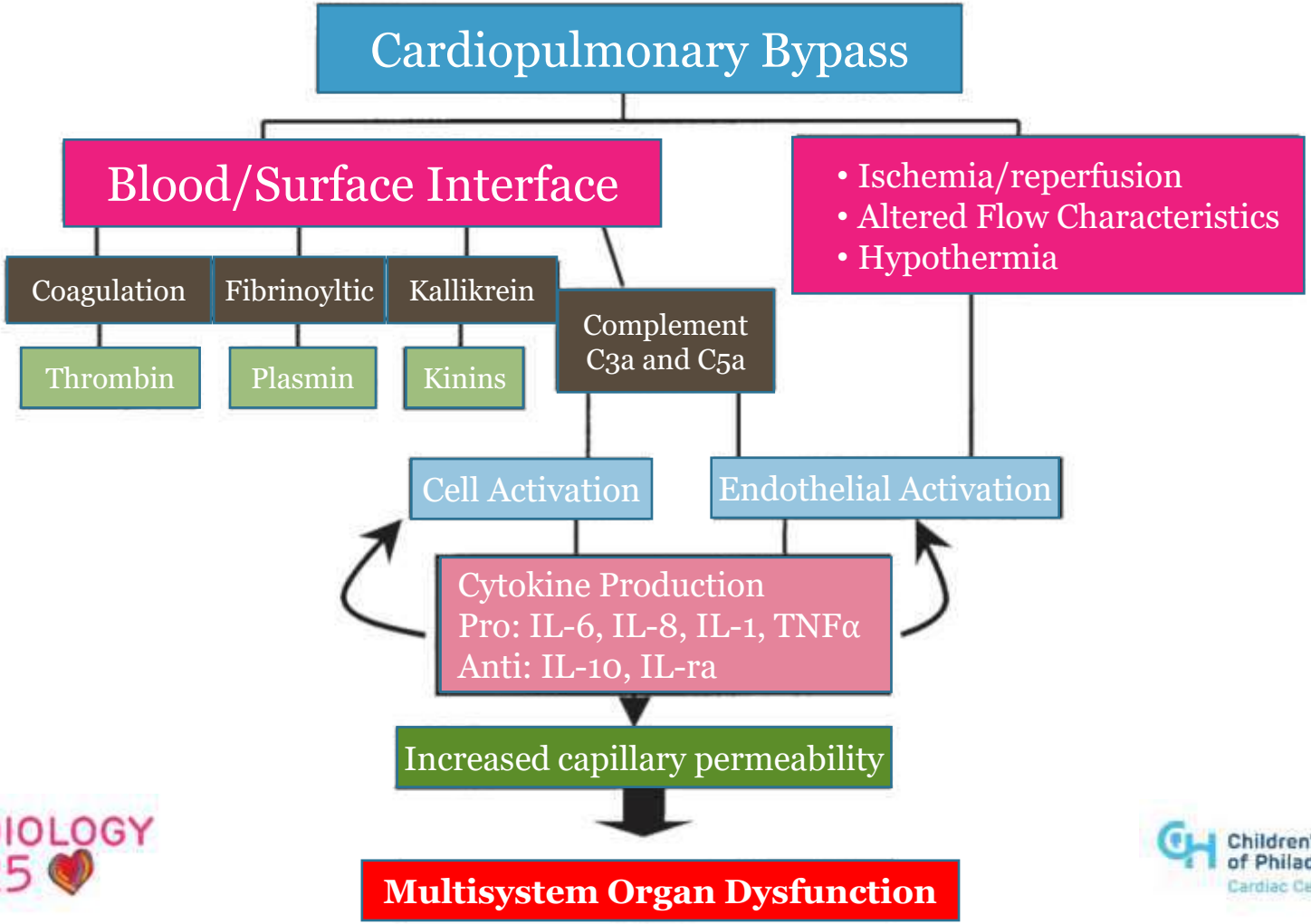

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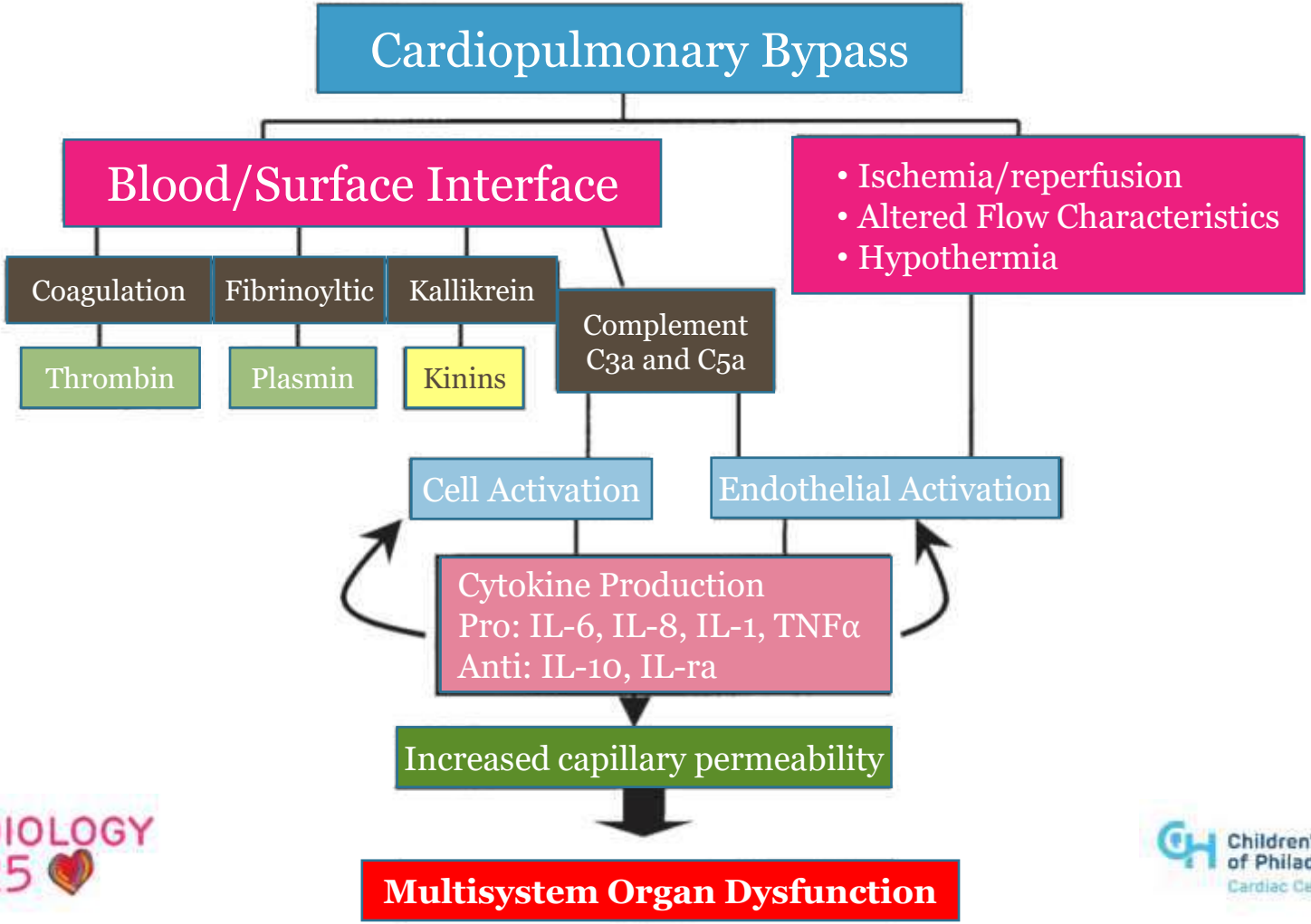

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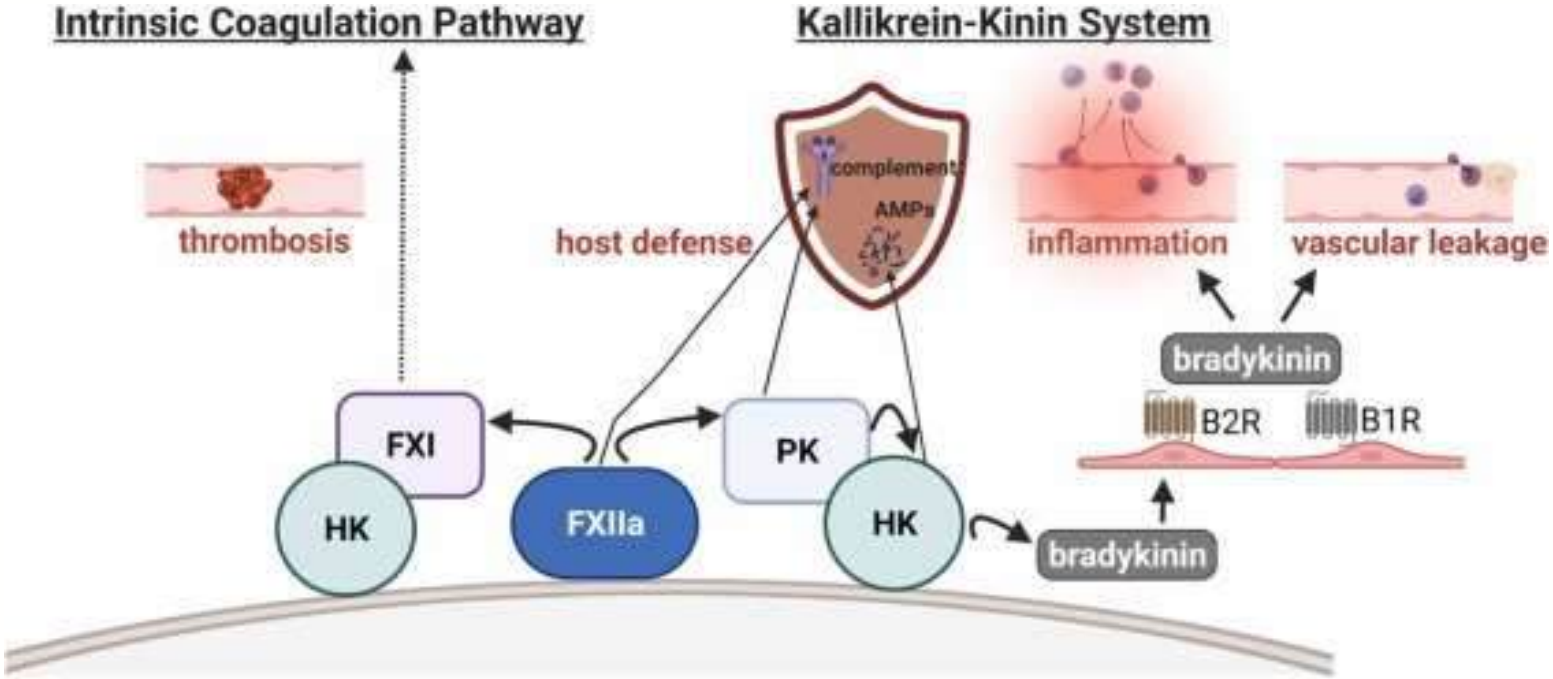
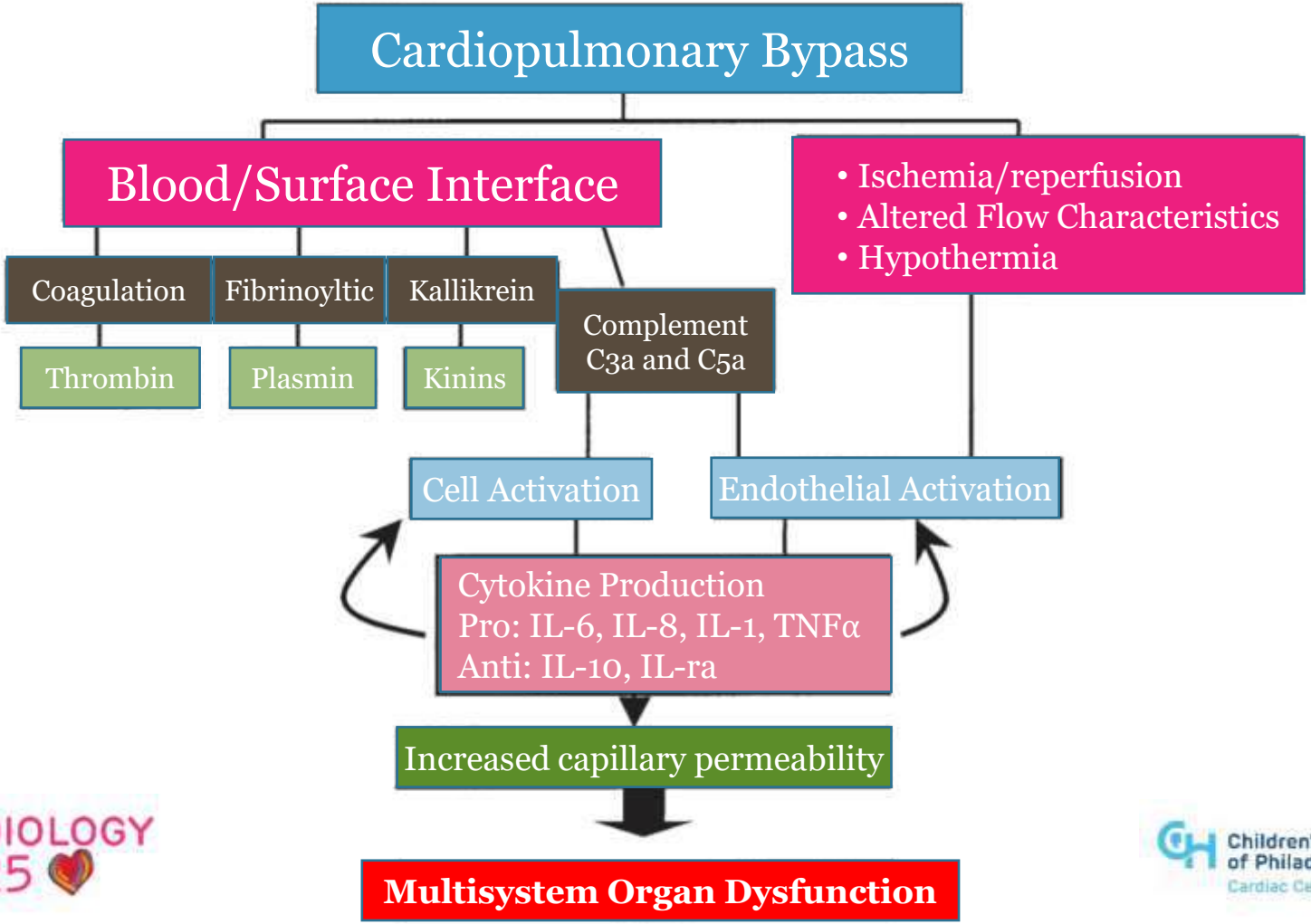
KININ PRODUCTION



Oehmcke-Hecht, 2022

Kozik and Tweddel, 2006



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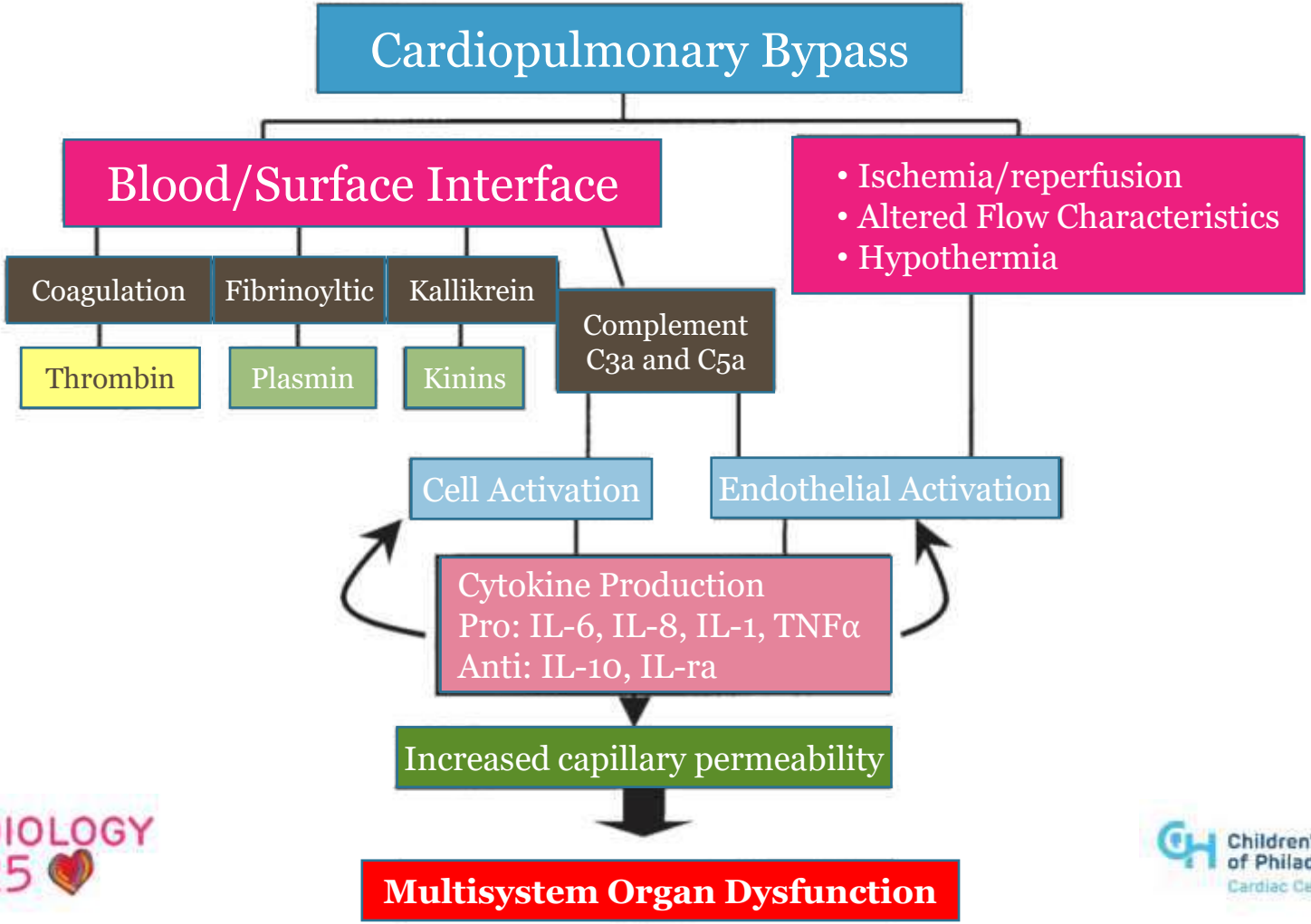

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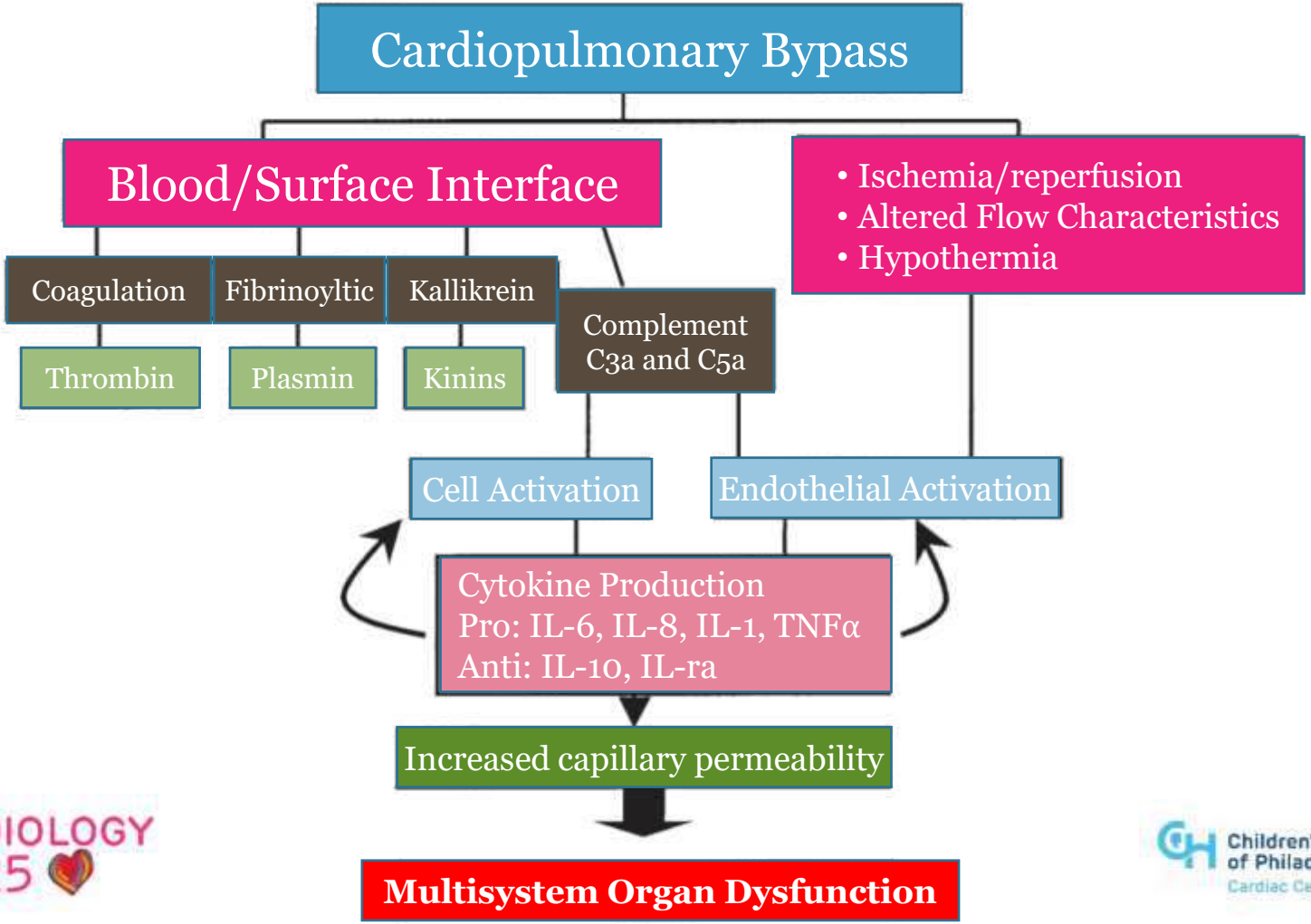
THROMBIN

- Triggered by **tissue factor** on activated endothelial cells and monocytes.
  - Heparin prevents clotting but does not stop thrombin activation.
- Thrombin amplifies inflammation by activating:
  - Platelets → Aggregation & clot formation.
  - Neutrophils → Adhesion, cytokine release, and tissue injury.
  - Endothelial cells → Increased vascular permeability & capillary leak.
- Exacerbates systemic inflammation, contributing to organ dysfunction.

Kozik and Tweddel, 2006



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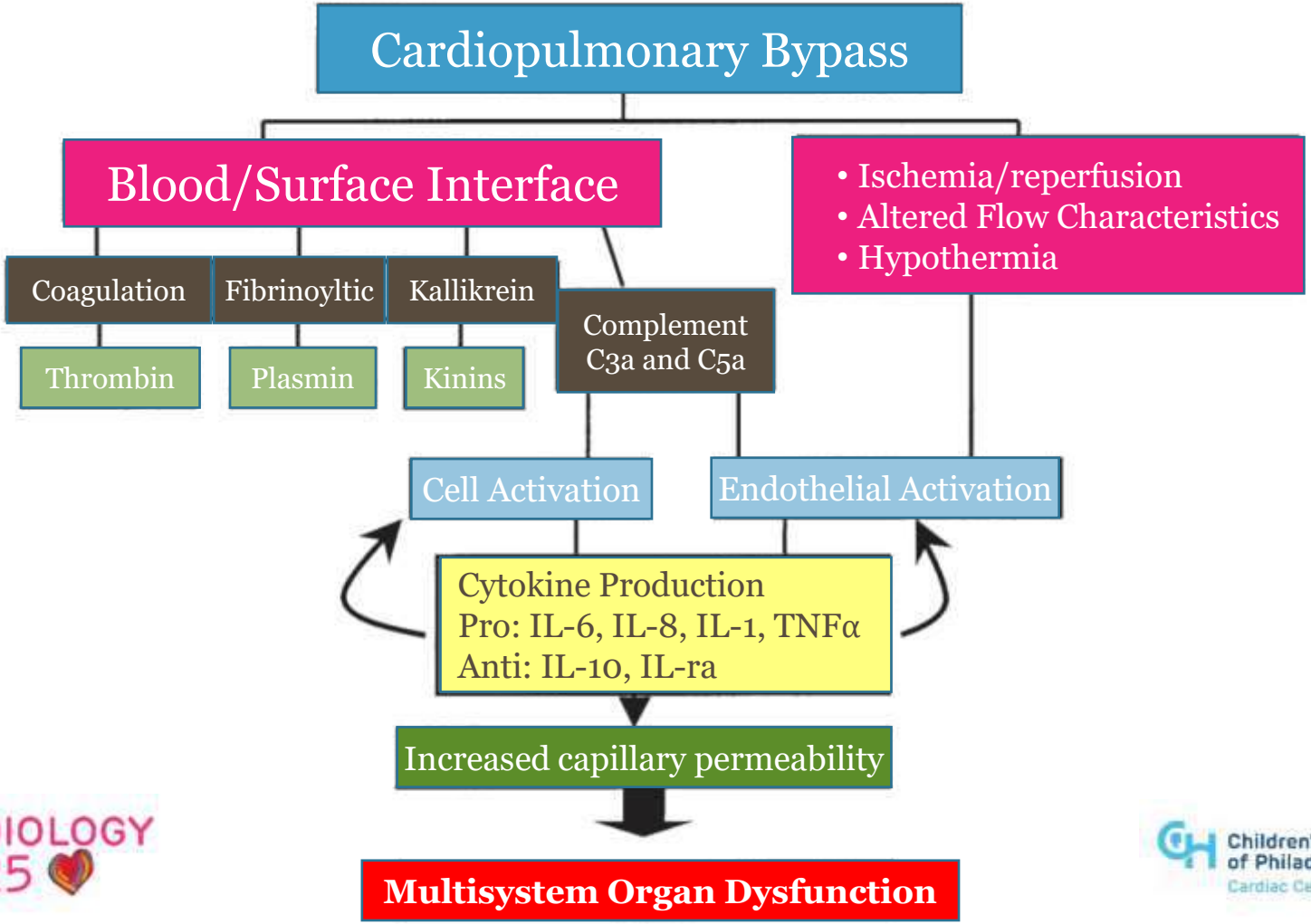

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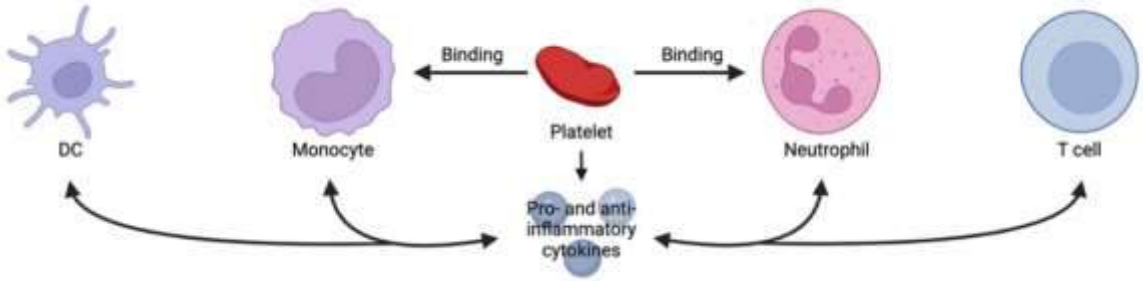
CYTOKINES

- **Pro-inflammatory cytokines** (TNF-α, IL-1, IL-6, IL-8) are upregulated, promoting inflammation, fever, and capillary leak.
- **Anti-inflammatory cytokines** (IL-10, IL-1ra) counteract excessive inflammation but may lead to **immune suppression**.
- **Higher IL-6 to IL-10 ratio** correlates with **worse outcomes** in children post-CPB.
- **IL-8 increases neutrophil activation and correlates with CPB duration**.



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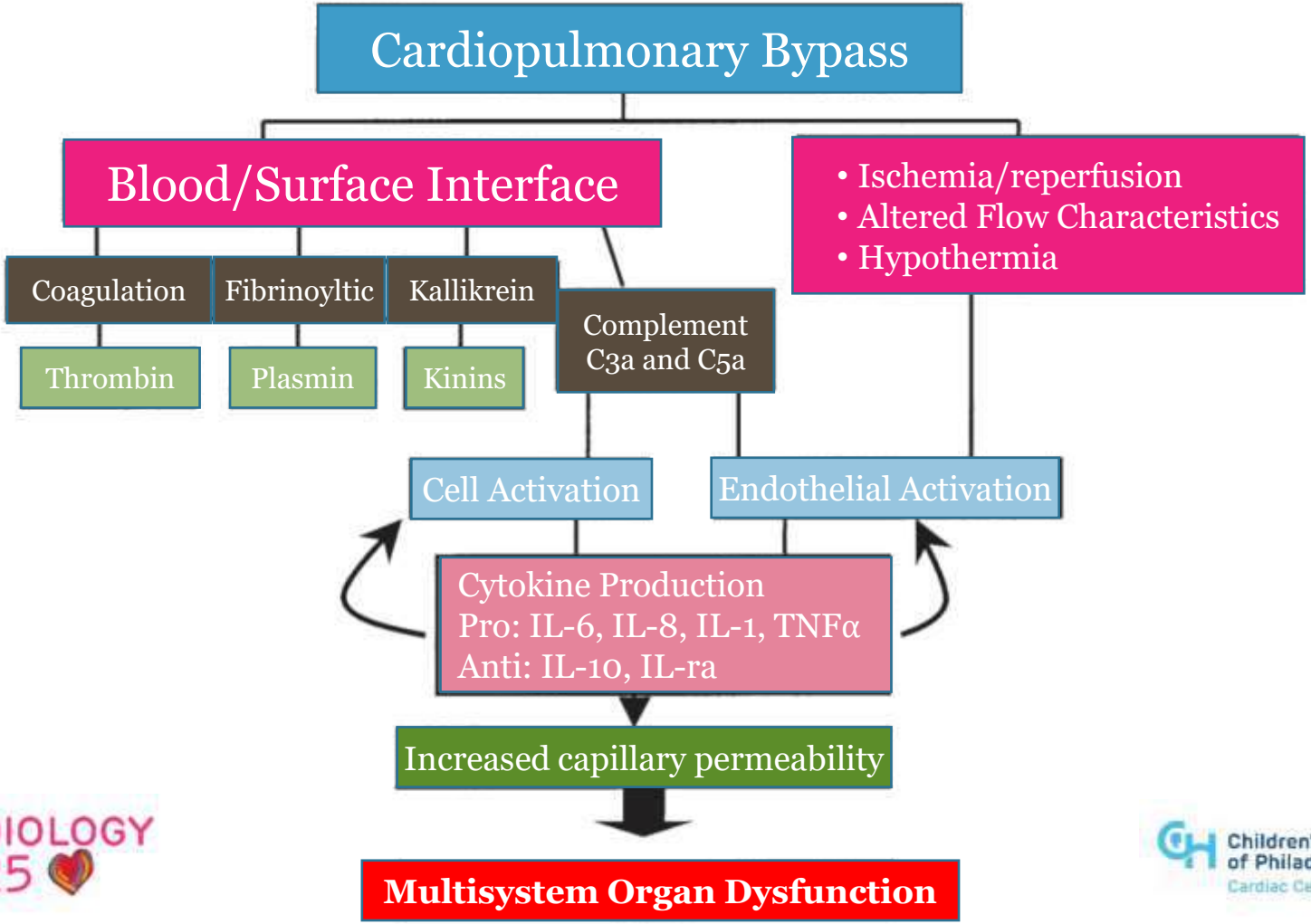

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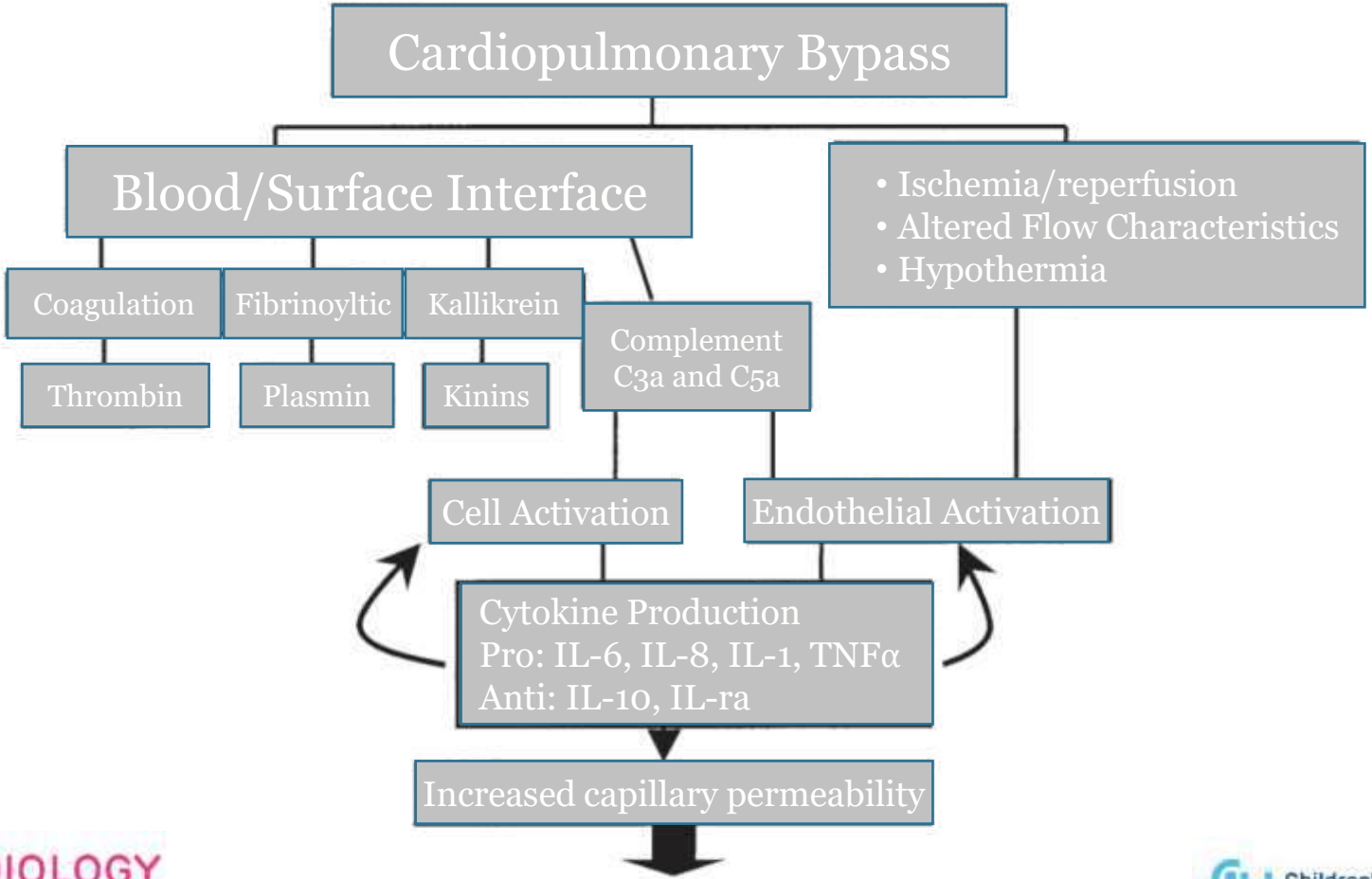

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Specific Organ System Dysfunction

CARDIAC DYSFUNCTION

Myocardial Injury & Ischemia-Reperfusion

- Aortic cross-clamping → ischemia-reperfusion injury
- Leukocyte & platelet activation → endothelial dysfunction
- TNF-α, IL-6, and IL-8 linked to myocardial dysfunction

Post-CPB Cardiac Dysfunction

- Reduced contractility due to inflammatory mediators
- Capillary leak → myocardial edema → impaired function
- Increased need for inotropic support postoperatively

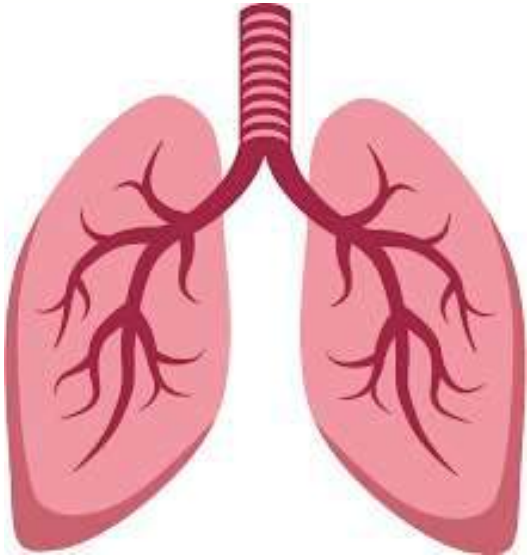
PULMONARY DYSFUNCTION

CPB Bypasses Normal Pulmonary Circulation

- Pulmonary circulation interrupted → endothelial injury
- Increased pulmonary vascular resistance (PVR)
- Loss of pulsatile flow → altered lung perfusion

Inflammatory Effects on the Lungs

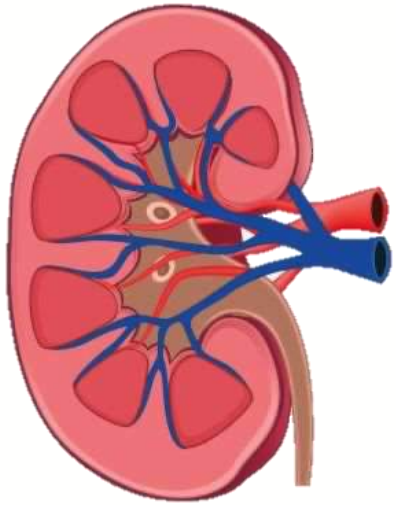
- Neutrophil sequestration → pulmonary edema
- Surfactant dysfunction → alveolar collapse
- Increased ventilation-perfusion (V/Q) mismatch → hypoxia



RENAL DYSFUNCTION

CPB-induced renal injury mechanisms:

- Hypoperfusion due to nonpulsatile flow and vasoconstriction
- Inflammatory mediators (TNF-α, thromboxane) reduce renal perfusion
- Immature neonatal kidney function impairs sodium & water regulation



Clinical consequences:

- Fluid overload → worsens pulmonary edema, delays extubation
- Electrolyte imbalances & acid-base disturbances
- Increased risk of acute kidney injury (AKI) and long-term renal impairment

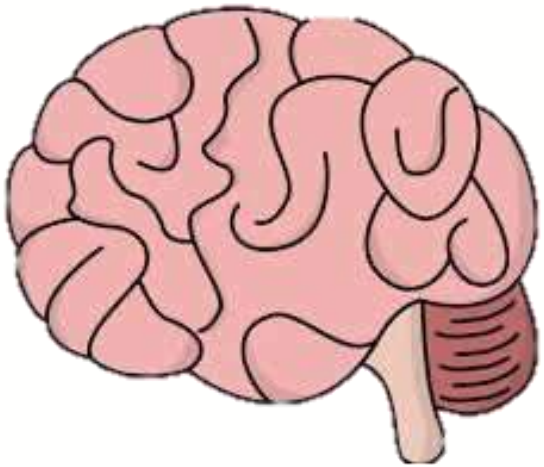
CEREBRAL DYSFUNCTION

Neonatal brain is highly vulnerable to CPB injury:

- High metabolic demand makes the brain sensitive to hypoxia
- Immature blood-brain barrier → increased permeability & cerebral edema

Mechanisms of cerebral injury:

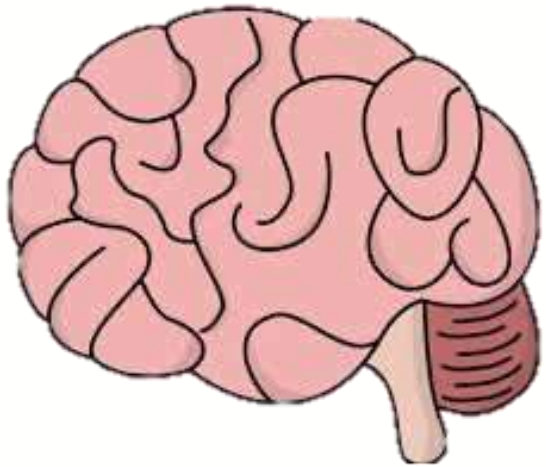
- Ischemia-reperfusion injury → oxidative stress, neuronal apoptosis
- Microemboli formation → linked to postoperative neurologic deficits
- Altered cerebral autoregulation → risk of hypoperfusion or hyperperfusion



CEREBRAL DYSFUNCTION - CONTINUED

Postoperative consequences:

- Increased risk of seizures, hypotonia, feeding difficulties
- Long-term effects: cognitive delays, motor deficits, and developmental issues



Strategies to modulate CPB-associated inflammatory response

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Non-pharmacologic

CPB CIRCUIT COATING AND OPTIMIZATION

- **Minimize Circuit Size**
  - Minimizing priming volume reduces hemodilution and inflammatory response.
  - Avoids excessive blood contact with artificial surfaces.
- **Surface-Coating**
  - Heparin – reduces complement activation
  - poly-2-methoxyethylacrylate - improves platelet preservation.
- **Leukocyte Filtration**

MODIFIED ULTRAFILTRATION

Removes low molecular-weight substances

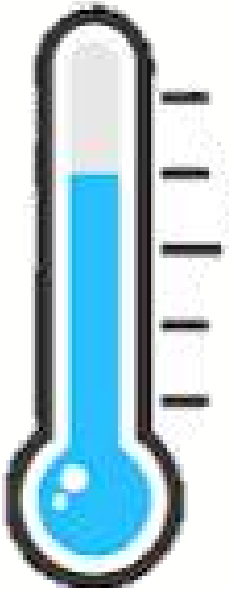
- Inflammatory cytokines (IL-6, IL-8, TNF-α)

Clinical Benefits

- Pulmonary benefits – improves lung compliance and gas exchange
- Cardiac benefits – reduces myocardial edema, improves contractility
- Lower transfusion needs

TEMPERATURE MANAGEMENT

- **Normothermia vs. Hypothermia**
  - Hypothermia (<34°C) increases vasoconstriction, myocardial afterload, coagulopathy, and bleeding
- **Controlled Rewarming**
  - Rewarming rate should be ≤0.5°C/min
    - Rapid rewarming can worsen the inflammatory response and cause neurologic and hemodynamic instability.



Strategies to modulate CPB-associated inflammatory response

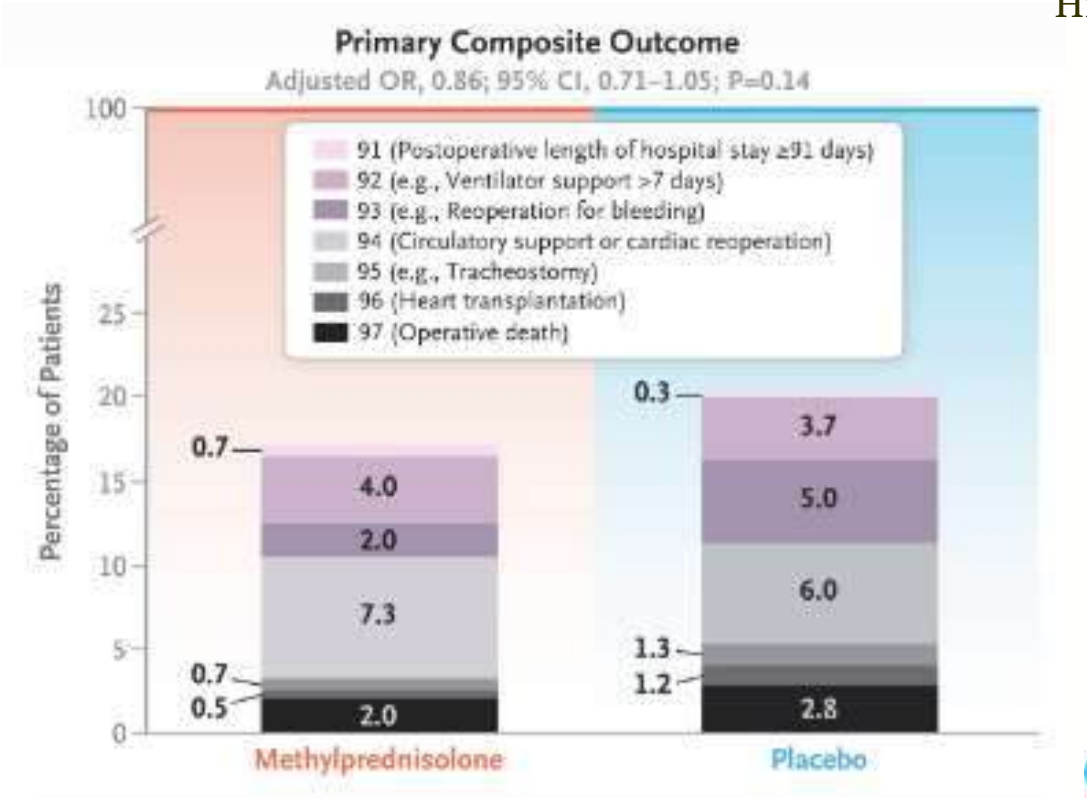
Pharmacologic

CORTICOSTEROIDS

- Suppress pro-inflammatory cytokine production (IL-6, IL-8, TNF-α).
- **Risks & Limitations**
  - Increased hyperglycemia
  - Potential immunosuppression
  - Possible association with delayed renal recovery.
- **Clinical Considerations**
  - No consensus on optimal dosing or timing.
  - May be beneficial in select subgroups but not universally recommended, practice varies widely

STEROIDS TO REDUCE SYSTEMIC INFLAMMATION AFTER INFANT HEART SURGERY – STRESS TRIAL

Hill et al. *NEJM*, 2022



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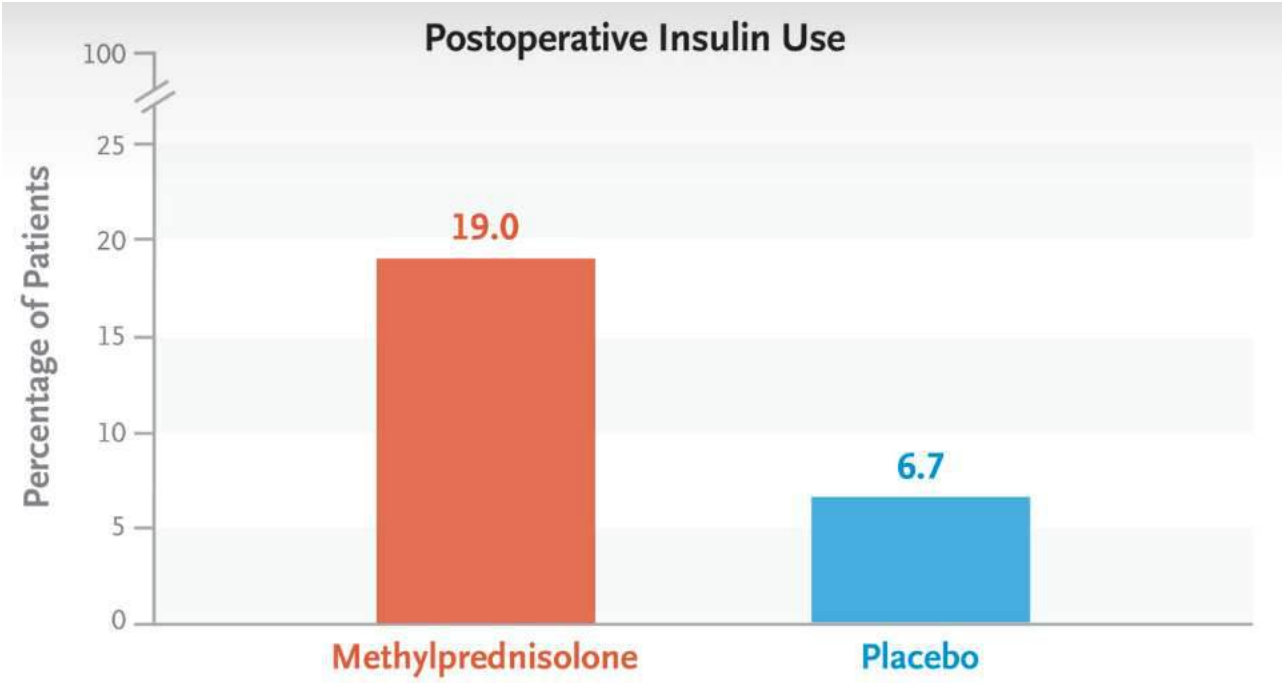

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ANTIFIBRINOLYTIC THERAPY

Commonly Used Antifibrinolytics

- Tranexamic Acid (TXA) – Lysine analog, inhibits fibrinolysis, reduces inflammatory response.
- Epsilon-Aminocaproic Acid (EACA) – Similar mechanism to TXA, used as an alternative.
- Aprotinin (Discontinued in Routine Use) – Previously used but withdrawn due to safety concerns (renal toxicity, thrombotic risk).

Reduces perioperative bleeding

- Prevents fibrinolysis by inhibiting plasminogen activation

Mitigates inflammatory response

- TXA shown to decrease inflammatory markers (e.g., D-dimer, PAI-1), reducing vasoplegia.

COMPLEMENT INHIBITORS

Common Complement Inhibitors

- Eculizumab – Monoclonal antibody targeting C5
- C1 Esterase Inhibitor (C1-INH) – Regulates classical pathway
- Nafamostat Mesylate – Inhibits complement and coagulation cascades

Clinical Considerations

- Limited pediatric data – Most studies in adults; ongoing research in pediatric cardiac surgery.
- Potential infection risk – Complement inhibition may increase susceptibility to infections.
- Expensive

NUCLEAR FACTOR KAPPA B (NF-κB) INHIBITORS

NF-κB controls inflammatory gene expression.

Reduces cytokine storm and systemic inflammation.

Limited pediatric data

Most research is preclinical or in adult models.

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Dexmedetomidine

Reduces incidence of AKI – potentially due to this mechanism

EMERGING THERAPIES

Leukocyte Modulation Devices

- Reduce leukocyte activation during and after bypass
- Reduced serum biomarkers of organ injury in pig models

Hemoabsorption Techniques – CytoSorb

- Mixed findings on effect on inflammatory markers and clinical outcomes

Targeting Shear Stress-Induced Inflammation

CONCLUSION

CPB triggers systemic inflammation, leading to **multi-organ dysfunction**.

Key inflammatory pathways: Complement activation, neutrophils, cytokines, endothelial dysfunction.

Impacts on major organs:

- **Heart** → Ischemia-reperfusion injury, myocardial dysfunction.
- **Lungs** → Pulmonary edema, impaired gas exchange.
- **Kidneys** → Hypoperfusion, AKI risk.
- **Brain** → Microemboli, neuroinflammation

Strategies to reduce inflammation:

- **Non-Pharmacologic:** MUF, controlled rewarming, heparin-coated circuits.
- **Pharmacologic:** Steroids (?), TXA, complement inhibitors

Multimodal approach optimizes outcomes, reducing inflammation, complications, and recovery time.

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Lake Buena Vista, Florida

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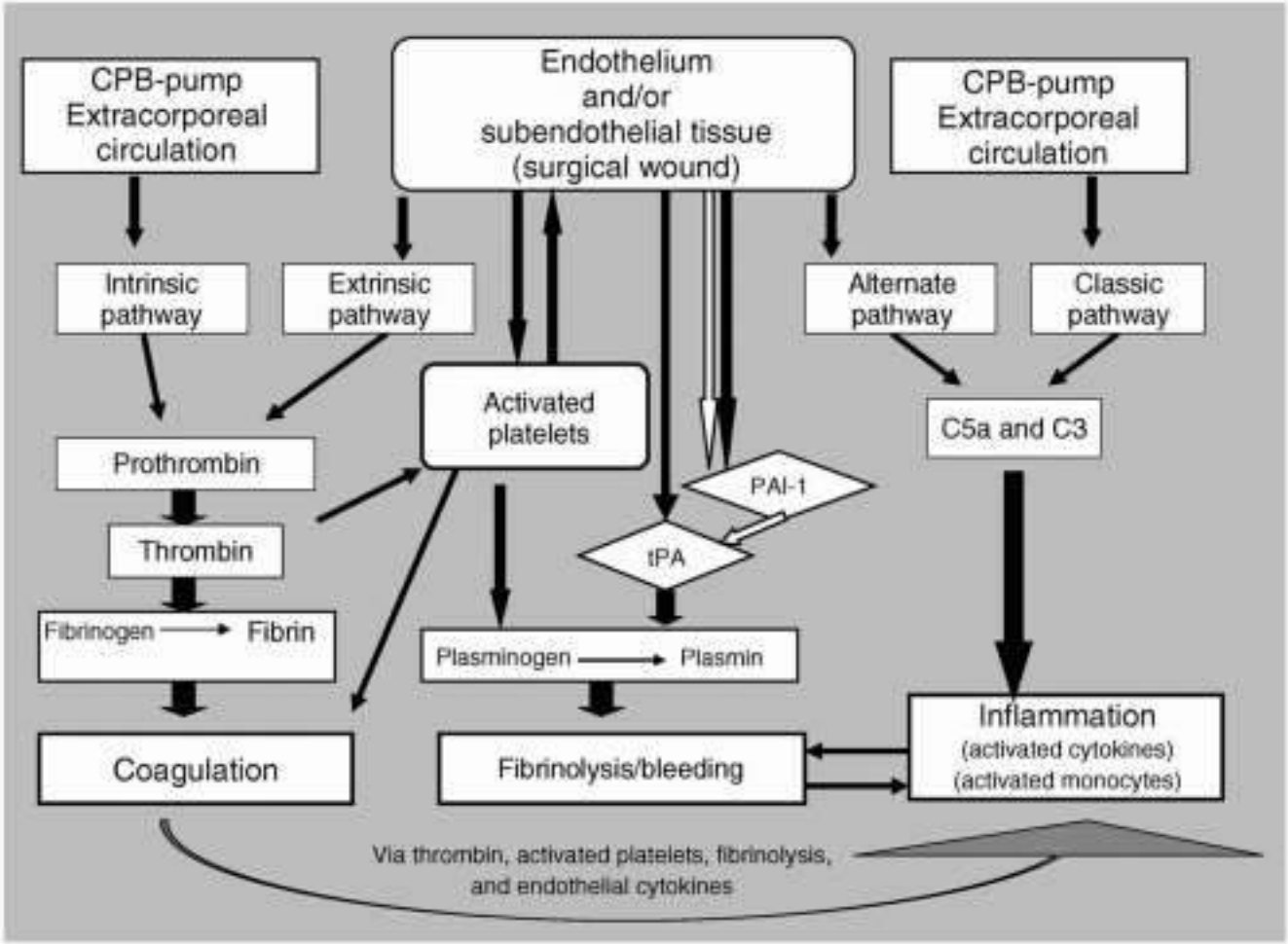
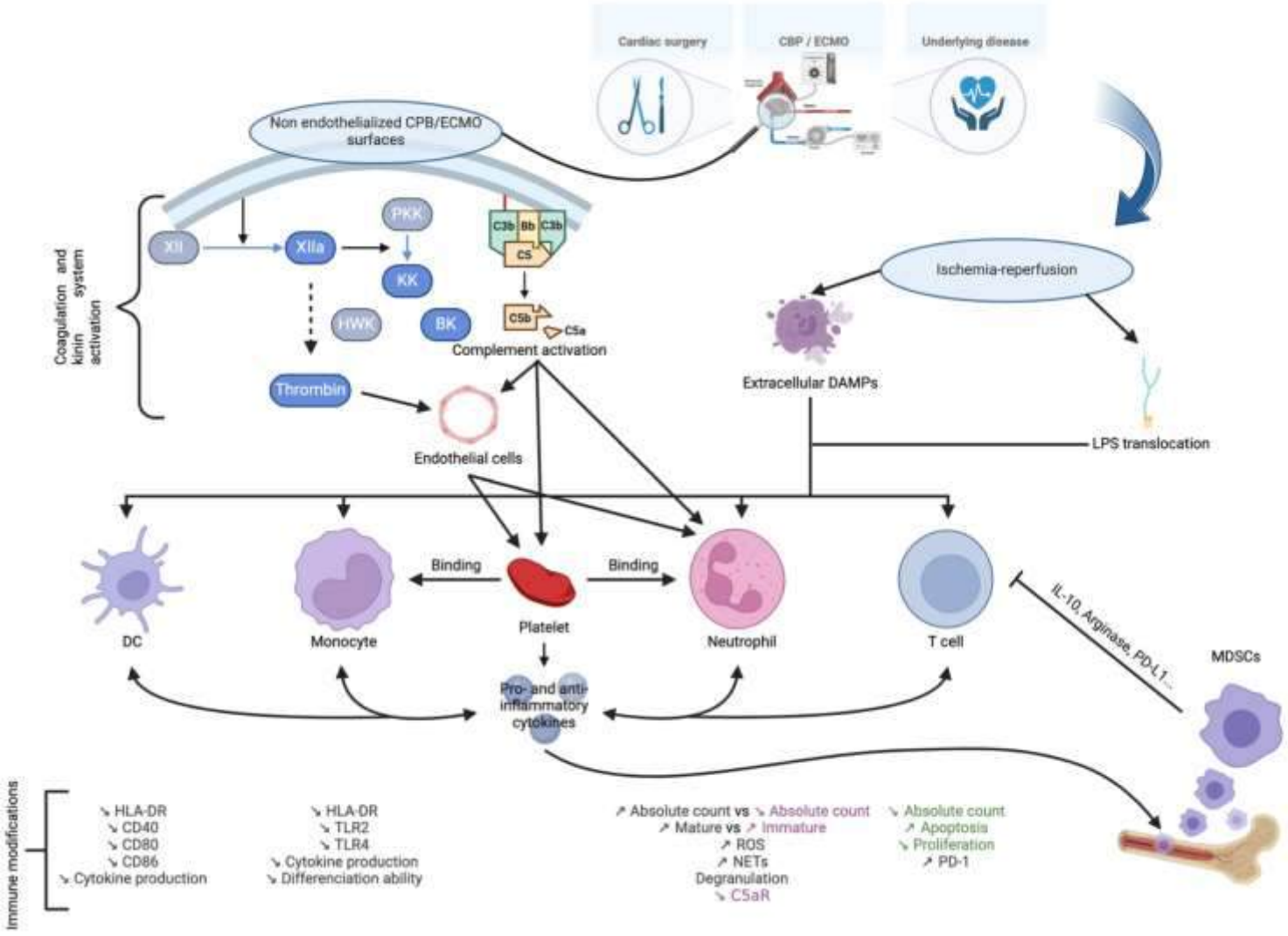
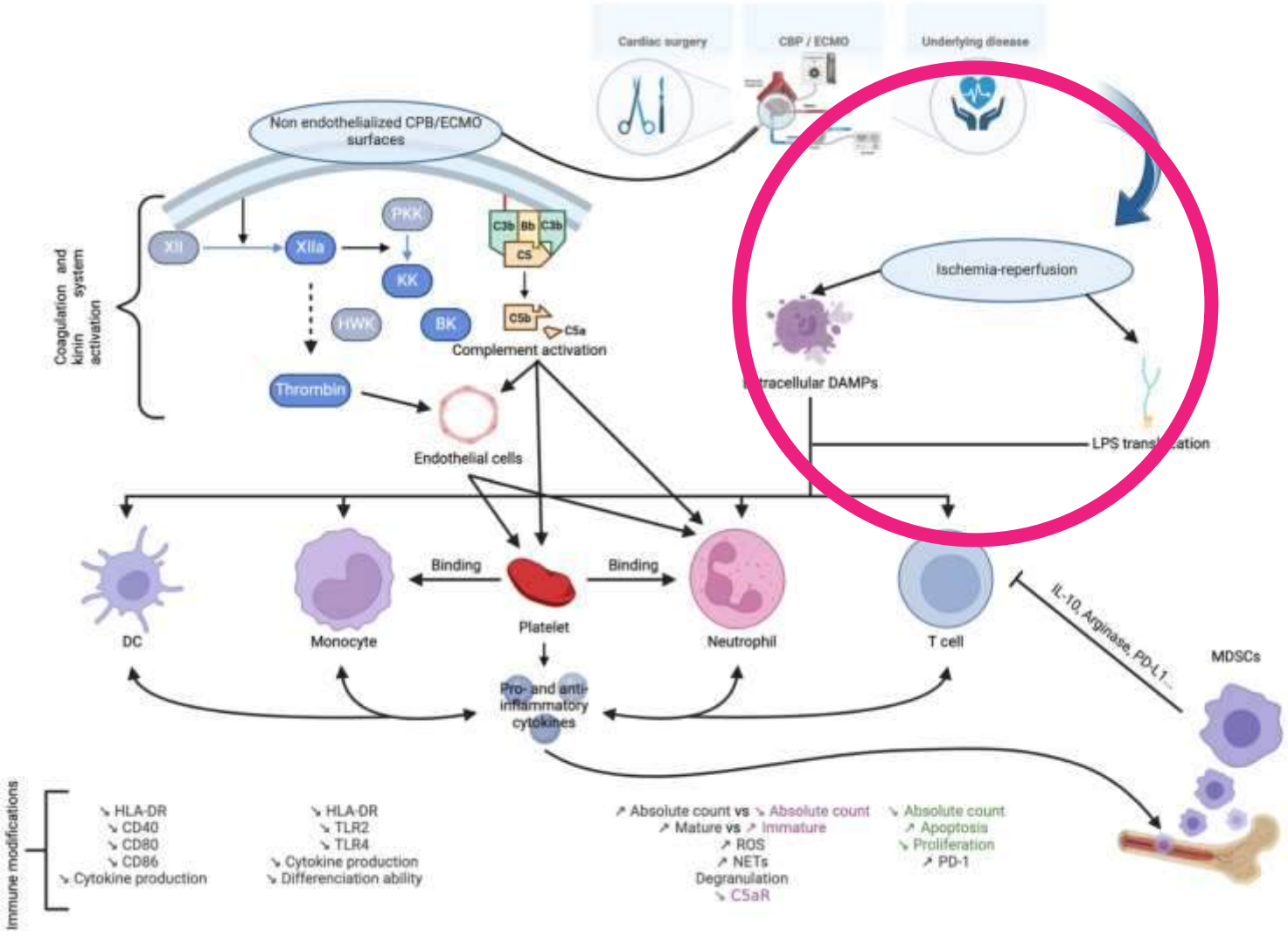

CPB-pump Extracorporeal circulation
Endothelium and/or subendothelial tissue (surgical wound)
CPB-pump Extracorporeal circulation
Intrinsic pathway
Extrinsic pathway
Alternate pathway
Classic pathway
Activated platelets
C5a and C3
Prothrombin
PAI-1
tPA
Thrombin
Fibrinogen → Fibrin
Plasminogen → Plasmin
Inflammation
(activated cytokines)
(activated monocytes)
Coagulation
Fibrinolysis/bleeding
Via thrombin, activated platelets, fibrinolysis, and endothelial cytokines


Cardiac surgery
CBP / ECMO
Underlying disease
Non endothelialized CPB/ECMO surfaces
Coagulation and kinin system activation
XII
XIIa
PKK
KK
HWK
BK
C3b
Bb
C3b
C5
C5b
C5a
Complement activation
Thrombin
Endothelial cells
Ischemia-reperfusion
Extracellular DAMPs
LPS translocation
DC
Monocyte
Binding
Binding
Platelet
Neutrophil
T cell
IL-10, Arginase, PD-L1...
MDSCs
Pro- and anti-inflammatory cytokines
Immune modifications
↘ HLA-DR
↘ CD40
↘ CD80
↘ CD86
↘ Cytokine production
↘ HLA-DR
↘ TLR2
↘ TLR4
↘ Cytokine production
↘ Differenciation ability
↗ Absolute count vs ↘ Absolute count
↗ Mature vs ↗ Immature
↗ ROS
↗ NETs
Degranulation
↘ C5aR
↘ Absolute count
↗ Apoptosis
↘ Proliferation
↗ PD-1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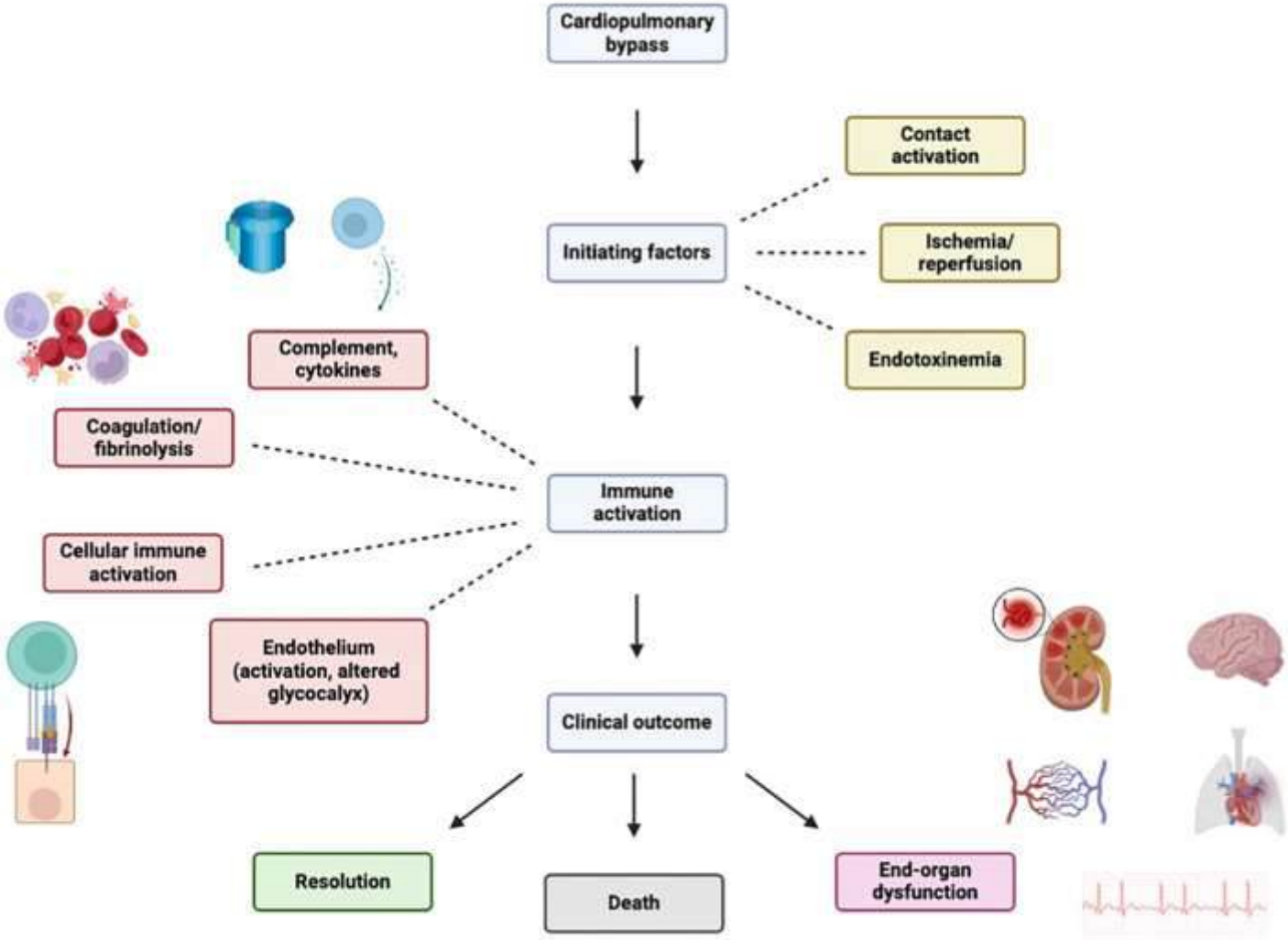
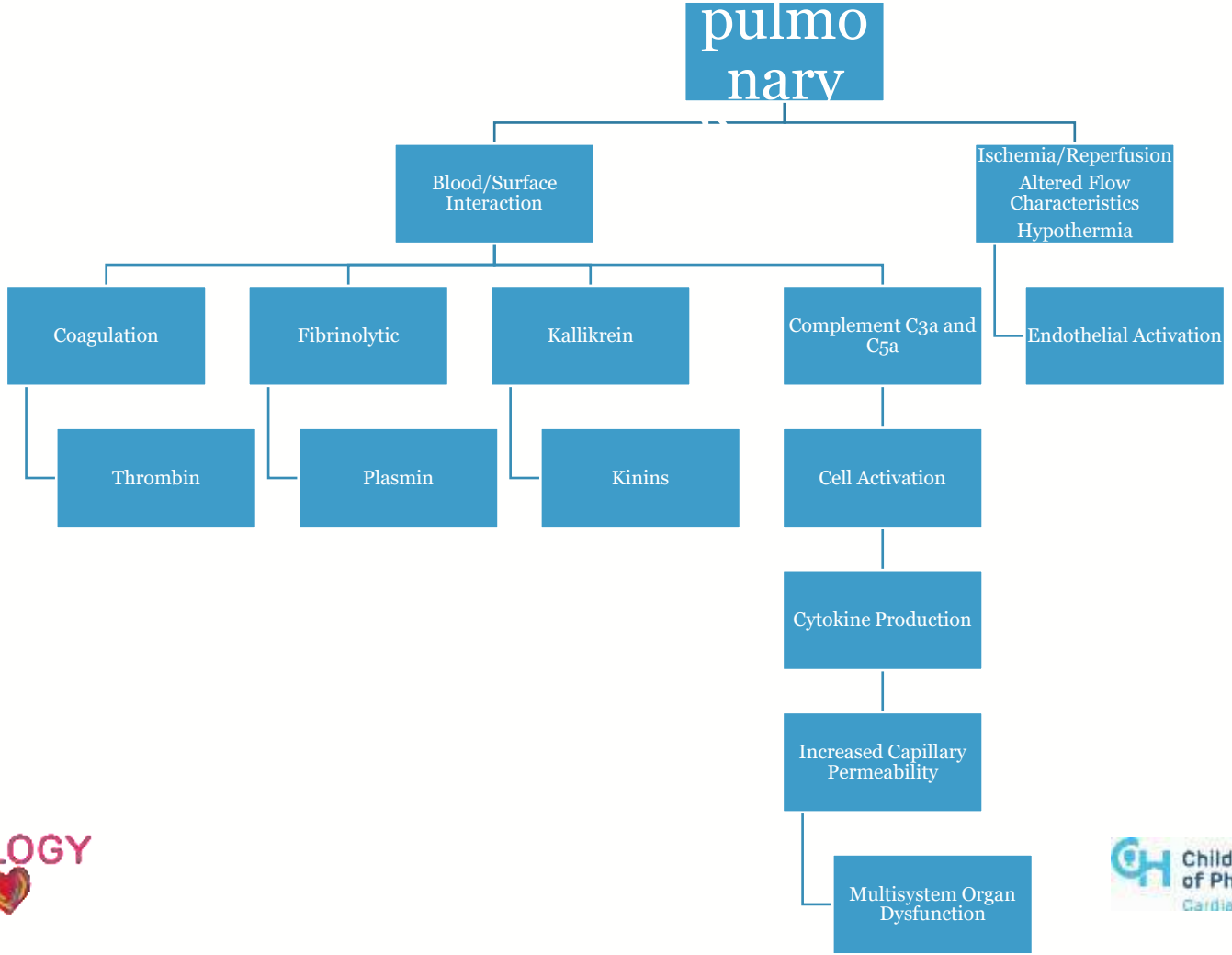

Cardiopulmonary bypass
Contact activation
Initiating factors
Ischemia/ reperfusion
Endotoxinemia
Complement, cytokines
Coagulation/ fibrinolysis
Immune activation
Cellular immune activation
Endothelium (activation, altered glycocalyx)
Clinical outcome
Resolution
Death
End-organ dysfunction



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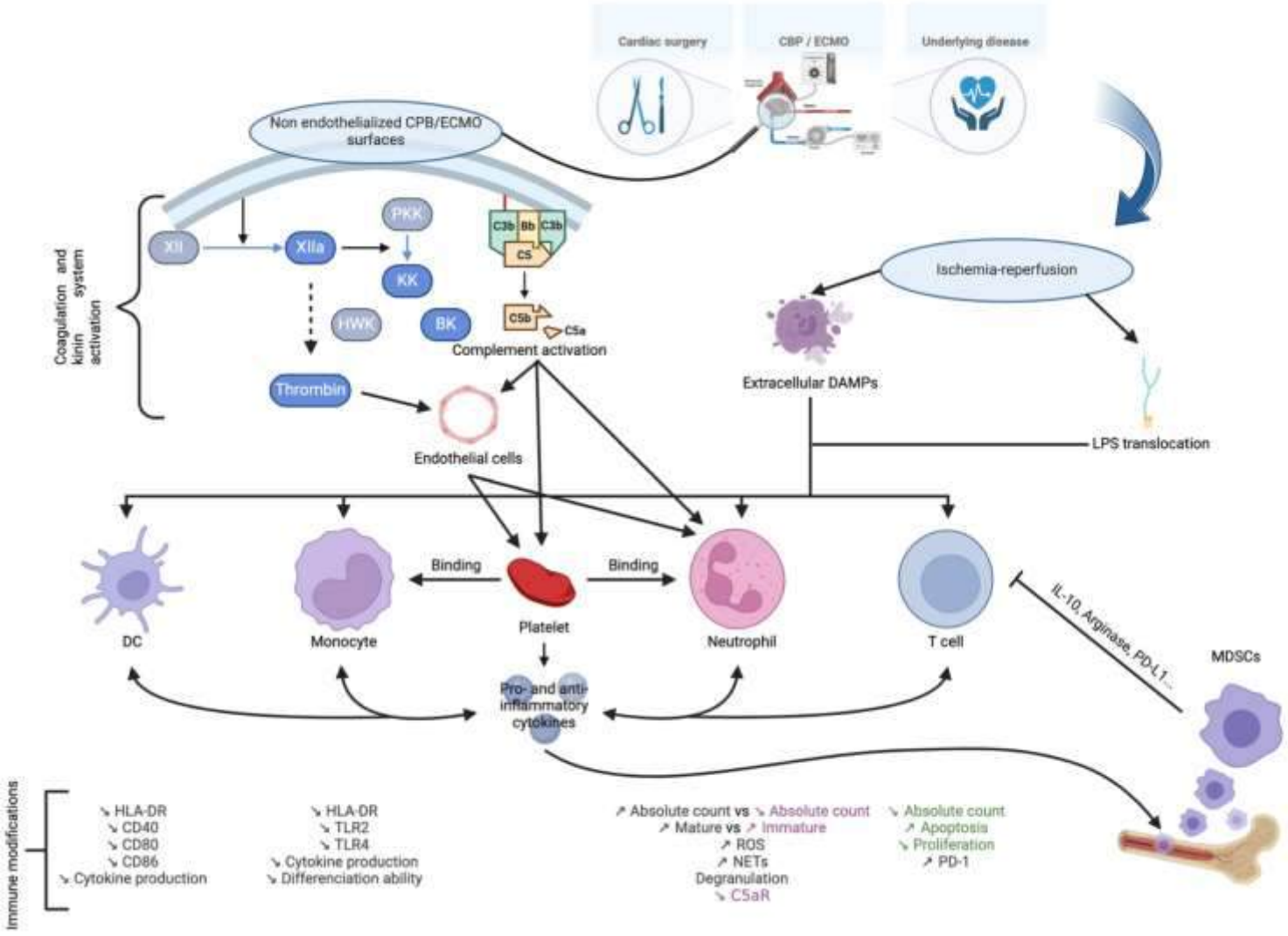
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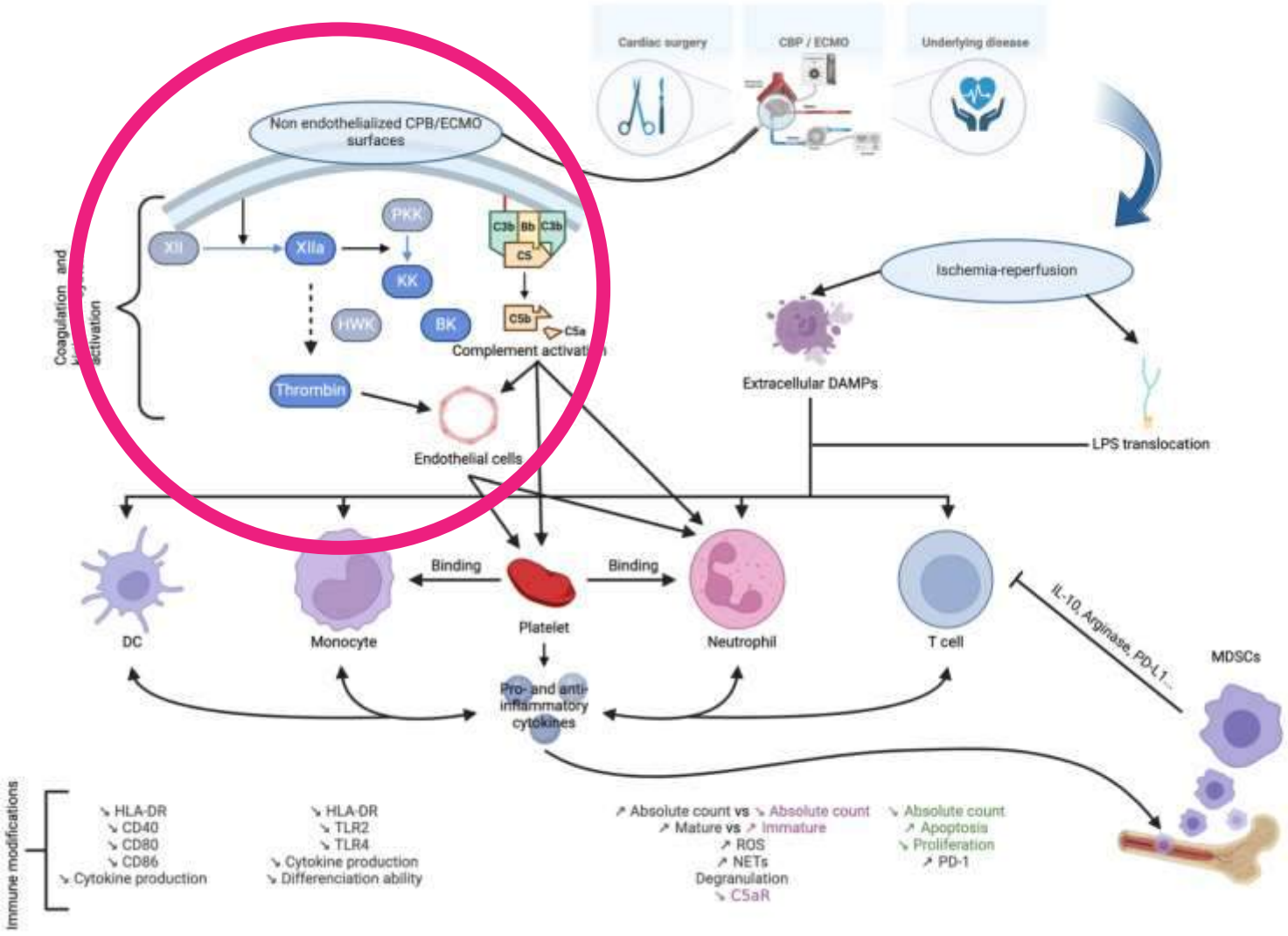
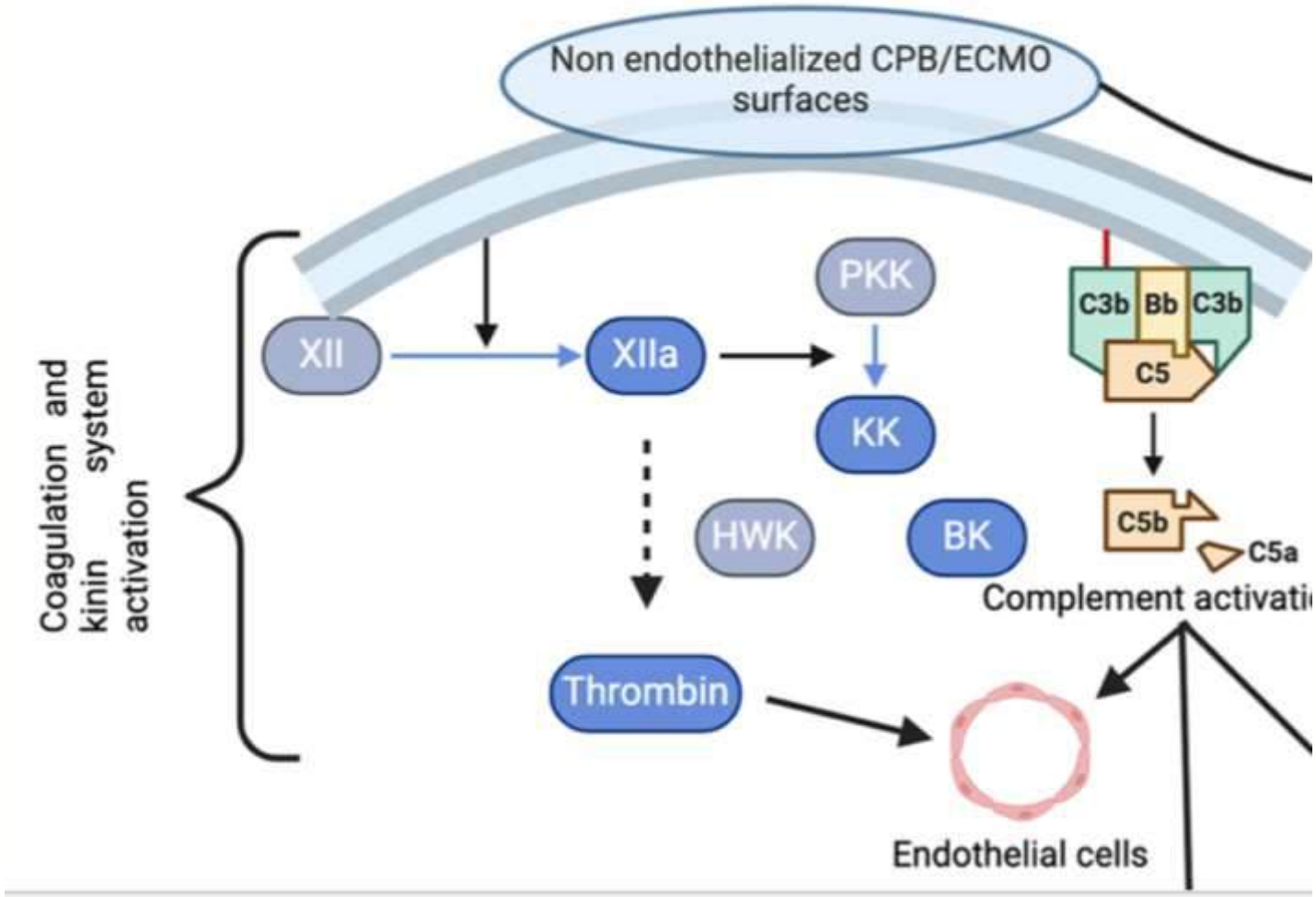
↗ PD-1


Cardiac surgery
CBP / ECMO
Underlying disease
Non endothelialized CPB/ECMO surfaces
Coagulation and activation
XII
XIIa
PKK
KK
HWK
BK
C3b
Bb
C3b
C5
C5b
C5a
Complement activation
Thrombin
Endothelial cells
Ischemia-reperfusion
Extracellular DAMPs
LPS translocation
Binding
Binding
DC
Monocyte
Platelet
Neutrophil
T cell
IL-10, Arginase, PD-L1...
MDSCs
Pro- and anti-inflammatory cytokines
Immune modifications
↘ HLA-DR
↘ CD40
↘ CD80
↘ CD86
↘ Cytokine production
↘ HLA-DR
↘ TLR2
↘ TLR4
↘ Cytokine production
↘ Differenciation ability
↗ Absolute count vs ↘ Absolute count
↗ Mature vs ↗ Immature
↗ ROS
↗ NETs
Degranulation
↘ C5aR
↘ Absolute count
↗ Apoptosis
↘ Proliferation
↗ PD-1


Non endothelialized CPB/ECMO surfaces
Coagulation and kinin system activation
XII
XIIa
PKK
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HWK
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C3b
Bb
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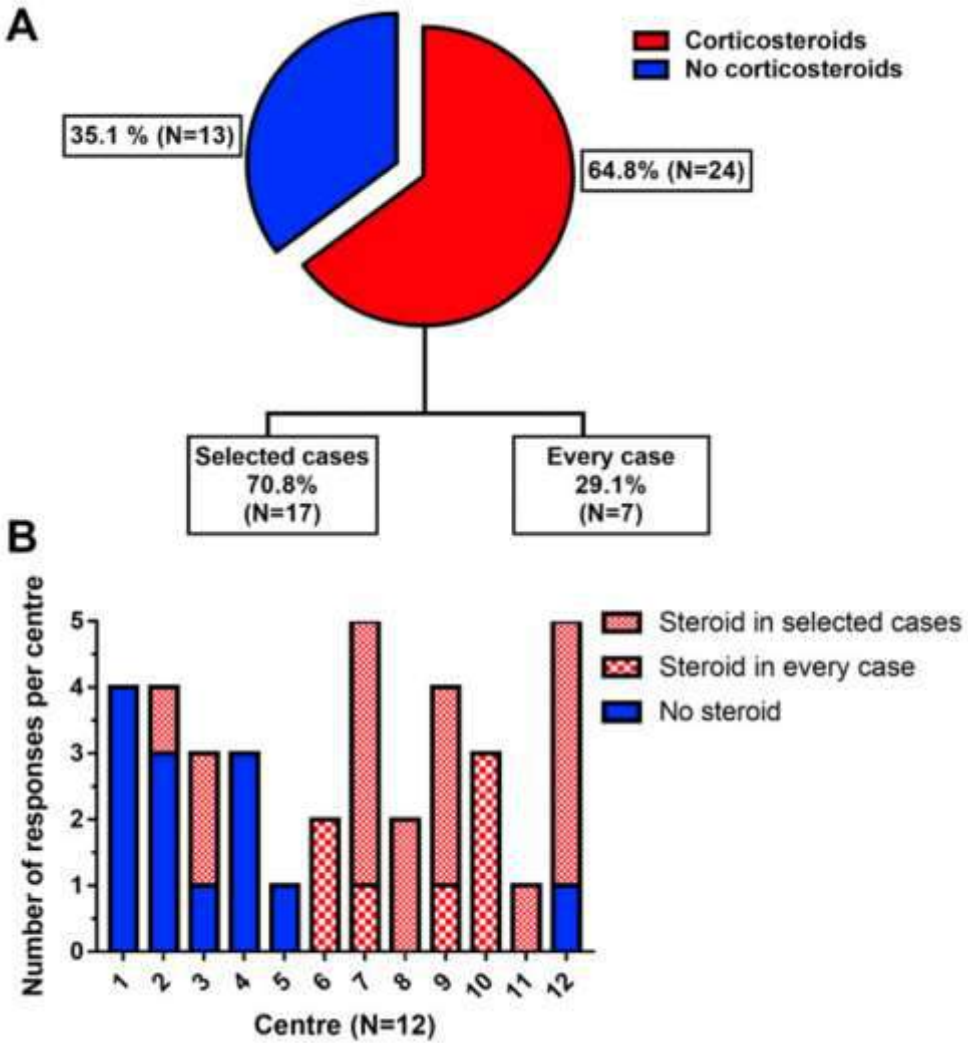
C5
C5b
C5a
Complement activati
Thrombin
Endothelial cells



CARDIOLOGY 2025

Children's Hospital of Philadelphia
Cardiac Center