Thrombocytopenia due to Uremia
Disclosure of Potential Conflict of Interest

I have no direct or indirect financial (or other) interests with companies whose products and/or services will be mentioned in this presentation. The material presented is for educational purposes only.
Thrombocytopenia vs. thrombocytopathy

Thrombocytopenia

Decreased platelet *count* (quantitative problem) is established as a risk for spontaneous bleeding, as well as for bleeding during a procedure.

Thrombocytopathy

Decreased platelet *function* (qualitative problem) also puts a patient at theoretical risk for spontaneous hemorrhage or procedure-related bleeding.
Problems may be hereditary or acquired

(a) Hereditary
   i) Glanzmann’s thrombasthenia
   ii) Bernard-Soulier Disease

(b) Acquired
   i) Uremia
   ii) Procedure-related (cardiac bypass)
   iii) Disease-related (hematologic disorders such as myelodysplasia)
   iv) Drug-related
      (1) Very common with modern pharmaceuticals for stroke prevention and other clot prevention
Problems may be hereditary or acquired

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Objectives

• Define uremia
• Clinical manifestations of uremia
• Normal platelet function
• Pathogenesis of platelet dysfunction in uremia
• Role of uremic toxins
• Role of nitric oxide
• Treatment
What is uremia?
Azotemia refers to high levels of urea or nitrogen (can be measured chemically, but no symptoms).

Uremia Clinicopathological manifestations of severe azotemia
What is urea?

Review of the urea cycle
The urea cycle takes place primarily in the liver, and to a lesser extent in the kidney.
PATHOPHYSIOLOGY OF RENAL INSUFFICIENCY:
Decreased glomerular filtration rate (GFR)

Failure of waste excretion

Elevated concentration of wastes in the blood stream
- incr. creatinine (Cr)
- incr. urea (blood urea nitrogen, BUN)
Clinical Manifestations of Uremia
Clinical features of uremia

- **Neural and muscular**
  - Fatigue, peripheral neuropathy, seizures, anorexia, nausea, decreased taste and smell, cramps, restless legs, sleep disturbance, daytime sleepiness, hiccups, coma, encephalopathy

- **Cardiovascular**
  - Hypertension, atherosclerosis, coronary artery disease, pericarditis, uremic fetor, peripheral and pulmonary edema

- **Skin**
  - Itching, skin dryness, uremic frost (excretion of urea through the skin)

- **Hematological**
  - Anemia, granulocyte and lymphocyte dysfunction, platelet dysfunction

- **Gastrointestinal**

- **Endocrine and metabolic**
  - Amenorrhea, altered levels of amino acids, bone disease by hyperphosphatemia, hyperparathyroidism, and vitamin D deficiency, reduced basal metabolic rate, insulin resistance, oxidative stress.

Azotemia is another word that refers to high levels of urea or a build up of azoles groups or nitrogen, but is used primarily when the abnormality can be measured chemically but is not yet so severe as to produce symptoms. Uremia is the pathological manifestations of severe azotemia.
# Clinical Manifestations of Bleeding Disorders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Platelet-type bleeding</th>
<th>Coagulation-type bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Spontaneous</td>
<td>Spontaneous</td>
</tr>
<tr>
<td></td>
<td>Following trauma, immediate</td>
<td>Following trauma, delayed</td>
</tr>
<tr>
<td>Location</td>
<td>Skin, mucous membranes (epistaxis, gingival hemorrhage, menorrhagia)</td>
<td>Deep soft tissue, joints (hemarthroses)</td>
</tr>
<tr>
<td>Cutaneous findings</td>
<td>Petechiae, purpura</td>
<td>Hematomas</td>
</tr>
</tbody>
</table>
Clinical/Lab Manifestations of Platelet Dysfunction in Uremia

- Most WHO Grade = 0
  - Most common w/bleeding: Grade 1
  - If Grade 3 occurs → injury or surgery

- Degree of azotemia doesn’t correlate w/ bleeding risk.

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No bleeding</td>
</tr>
<tr>
<td>1</td>
<td>Minor bleeding (petechiae, ecchymoses, blood in secretions, vaginal spotting)</td>
</tr>
<tr>
<td>2</td>
<td>Gross hemorrhage not requiring RBC transfusion (epistaxis, hematemesis, hematuria)</td>
</tr>
<tr>
<td>3</td>
<td>Gross hemorrhage requiring 1+ RBCs per day</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening hemorrhage (bleeding causing hemodynamic compromise or into vital organ, like head/lungs/heart)</td>
</tr>
</tbody>
</table>

Azotemia is another word that refers to high levels of urea, but is used primarily when the abnormality can be measured chemically but is not yet so severe as to produce symptoms. Uremia is the pathological manifestations of severe azotemia.
• *In vitro* coagulation tests normal

• +/- thrombocytopenia

• Platelet function tests – abnormal
Normal Platelet Function

Urea indirectly disrupts platelet adherence, platelet activation, and platelet aggregation. So, it is important to know how platelets are normally activated.
PLATELET ADHESION

Damaged endothelium

Low shear stress conditions: plts can bind to collagen directly via GP Ia/Ila on plt surface
DG = diacylglycerol; IP₃ = inositol trisphosphate; P2Y₁, P2Y₁₂ = G-protein-coupled ADP receptors; PIP₂ = phosphatidylinositol bisphosphate; PKC = Protein kinase C
<table>
<thead>
<tr>
<th><strong>Alpha Granules</strong></th>
<th><strong>Dense Bodies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>ADP</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>Calcium</td>
</tr>
<tr>
<td>Factor V &amp; vWF</td>
<td>Histamine</td>
</tr>
<tr>
<td>Platelet factor 4</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Platelet-derived growth factor (PDGF)</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>P-selectin</td>
<td></td>
</tr>
<tr>
<td>Beta-thromboglobulin</td>
<td></td>
</tr>
<tr>
<td>Thrombospondin</td>
<td></td>
</tr>
</tbody>
</table>
PLATELET AGGREGATION

Platelet activation

Granule secretion

Lesser role: plt cross linking via: GPIIb/IIIa --- VWF --- GPIIb/IIIa
• Urea indirectly:
  
  – Causes platelet dysfunction
  
  – Inhibits platelet activation
Pathogenesis of Platelet Dysfunction in Uremia
• Uremic Toxins*
  – Abnormal plt adhesion/aggregation
    • Abnormal expression of glycoproteins
    • vWF abnormalities
  – Defective scramblase activity

• Abnormal production of nitric oxide*
  – Defective scramblase activity
  – Platelet activation issues:
    • Abnormal dense granule release & contents (esp. ADP & serotonin)
    • Abnormal $\alpha$-granule release
    • Defective cyclooxygenase activity/arachidonic acid

• Anemia
  – Erythropoietin deficiency
  – Platelet function issues

* Alternative pathways to detox ammonia
Uremic Toxins
• **Urea does not cause uremic platelet dysfunction**
  – No predictable correlation between the urea concentration (or BUN) & bleeding time

• **Guanidinosuccinic acid & methylguanidine** → suggested toxins
Abnormal expression of glycoproteins
<table>
<thead>
<tr>
<th>Adhesive Platelet Membrane Glycoproteins</th>
<th>Gene Family</th>
<th>Ligand</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP IIb/IIIa</td>
<td>Integron</td>
<td>Fibr, vWF, FN, VN</td>
<td>Aggregation</td>
</tr>
<tr>
<td>Vitronectin receptor</td>
<td>Integron</td>
<td>VN, ?vWF, fibr</td>
<td>Adhesion</td>
</tr>
<tr>
<td>GP Ic/IIa</td>
<td>Integron</td>
<td>FN, laminin</td>
<td>Adhesion</td>
</tr>
<tr>
<td>α6/IIa</td>
<td>Integron</td>
<td>Laminin</td>
<td>Adhesion</td>
</tr>
<tr>
<td>GP Ia/IIa</td>
<td>Integron</td>
<td>Collagen</td>
<td>Adhesion</td>
</tr>
<tr>
<td>GP Ib/IX</td>
<td>Leucine-rich glycoprotein</td>
<td>vWF, THR</td>
<td>Adhesion</td>
</tr>
<tr>
<td>P-Selectin</td>
<td>Selectin</td>
<td>PSGL-1, O-linked carbohydrate</td>
<td>Platelet-leukocyte interactions</td>
</tr>
<tr>
<td>PECAM-1</td>
<td>Immunoglobulin</td>
<td>?</td>
<td>Platelet-endothelial cell interactions</td>
</tr>
<tr>
<td>GP IV</td>
<td>?</td>
<td>TSP, Collagen</td>
<td>Adhesion</td>
</tr>
<tr>
<td>GP VI</td>
<td>?</td>
<td>Collagen</td>
<td>Signaling</td>
</tr>
<tr>
<td>PETA-3</td>
<td>Tetraspan</td>
<td>?</td>
<td>? Aggregation</td>
</tr>
</tbody>
</table>
PLATELET ADHESION

Low shear stress conditions: platelets can bind to collagen directly via GP Ib/IX/V on platelet surface.

Damaged endothelium

Collagen Exposure

GP Ib/IX/V

X

VWF
Lesser role: plt cross linking via:
GPIIb/IIIa --- VWF---GPIIb/IIIa
Abnormal expression of Scramblase
• Toxins directly interfere

• Lack of calcium influx due to NO
INTERACTION OF PLATELETS & COAGULATION FACTORS

Subendothelial cell w/ TF exposure

IX → IXa + VIII → Xa → IIa → fibrinogen → fibrin

Activated Platelet

TF / VIIa

VIII | | V

VII | | V

Aminophospholipid
Nitric Oxide
The Urea cycle involves the conversion of arginine into urea. The cycle starts with arginine, which is converted into ornithine. Ornithine is then converted into citrulline. Citrulline enters the mitochondria and is converted into argininosuccinate. Argininosuccinate is then converted into arginine. The cycle continues with the release of carbon dioxide and ammonia, leading to the production of urea.
NO
Soluble guanylyl cyclase

GTP

GTP

NO

Nitroprusside
Nitrosothiol
Organic nitrates
Etc

Guanylyl cyclase

Vasodilation
Platelet inhibition
Smooth muscle regulation
Immune regulation
Etc

Adenylyl cyclase

ATP

Adenylyl cyclase

ATP

AMP

phosphodiesterase 3

Inositol trisphosphate (IP₃)

Ca²⁺

Protein Kinase C

Pleckstrin

Pleckstrin-P

Inositol trisphosphate (IP₃)

IRAG

Inositol 1,4,5 triphosphate receptor-associated protein

cGMP-dependent protein kinases

phosphodiesterase 3

cGMP

cGMP

cGMP

cGMP

cyclic guanosine monophosphate

GTP

GTP
Anemia & Platelet “Dysfunction”
Renal Disease: Decreased renal EPO production

X +/- in uremia
• Hematocrit > .30 L/L → rbc occupy center of vessel & plts skim at the endothelial surface
• Anemia → plts are dispersed → impairing adherence to endothelial surface
• Correction of anemia w/ transfusions or erythropoietic stimulating agents → gives the plts a fighting chance
Treatment
• Uremia + active bleeding
  – Raising the hgb >100 g/L
  – Desmopressin (dDAVP)
  – Cryoprecipitate
  – Dialysis: 1] Prevents uremia 2] Corrects bleeding time in 2/3 pts w/ uremic bleeding
    – Hemodialysis or peritoneal

• Long-term:
  – Estrogens
  – Dialysis

• Incr. hgb (if low) → dDAVP → No response → cryoprecipitate.
Desmopressin (dDAVP)

• Increases release of FVIII:vWF multimers from endothelial cells
• May enhance glycoprotein expression
• Dose:
  – 0.30 mcg/kg [IV (w/ 50 mL saline over 15-30 minutes) or intranasally]
    • Effects begins w/n 1hr
    • Last 4 -24 hrs

Desmopressin: analog of antidiuretic hormone w/ little vasopressor activity
**Correction of Anemia**

- **Goal** → Hgb > 100 g/L or hct > 30%
  - Acute: RBC transfusions *
  - Chronic: Erythropoietic stimulating agents (ESAs)
    - Darbepoetin alfa and epoetin

- **Platelet Function Improvement ??**
  - ESA may incr. the # of GP IIb/IIIa
  - Enhancement of Gq protein
  - Enhancement of Ca++ uptake

*No prospective randomized studies that directly compared outcomes with erythropoietic agents versus red blood cell transfusions in patients with anemia and CKD
Conjugated Estrogens

- 17-β estradiol thought to act by influx of Ca++
  - May decrease generation of NO
- Controls chronic bleeds
- Dose: IV (0.6 mg/kg q1dX5); Oral (2.5-25 mg/day); Transdermal (100 mcg)
- Peak 5-7 days; Effects 1 weeks after discontinued.
- Limited safety data for use in men
Cryoprecipitate

- 6 units
- Improvement seen w/n 1 hr; last 4-24 hrs.

**Volume:** 15 mL
**Contents:**
- ≥ 150 mg fibrinogen
- ≥ 80 IU Factor VIII
- 80-120 IU vWF
- 40-60 IU Factor XIII
- Fibronectin
Role of Platelets
End
References


• Viganò G, Zoja C, Corna D, et al. 17 beta-estradiol is the most active component of the conjugated estrogen mixture active on uremic bleeding by a receptor mechanism. J Pharmacol Exp Ther 1990; 252:344.