Hepatic Sinusoidal Obstruction Syndrome
Formerly known as Veno-occlusive Disease

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OBJECTIVES
• What is HSOS/VOD?
• What are the key risk factors?
• How do we monitor for SOS and how can we mitigate the risk?
• How do we treat it?

Disease history
• First diagnosed in BMT patients in 1980.
  • Associated with myeloablative conditioning (e.g., CY/TBI, or BU/CY/TBI).
  • Initial autopsies showed hepatic venular occlusion, giving rise to initial name “veno-occlusive disease”.
• Later autopsies showed:
  • Not all patients had venular occlusions
  • Damage occurs first in the sinusoids
  • Coagulation is coincident not causative
• Newer proposed name of Hepatic Sinusoidal Obstruction Syndrome

Risk of mortality
• Depends on severity
• Severe HSOS results in Multi Organ Failure (MOF)
  • MOF develops in 30-50% of patients with post transplant HSOS
  • Overall Mortality in SOS with MOF: >80% if untreated

Cause of death: Multisystem Organ Failure
• Hypoalbuminemia causes ascites
  • Results in hypoventilation → pulmonary failure
  • Renal vasoconstriction → renal failure
• Decreased clotting factors → hemorrhage
• Damaged sinusoidal endothelial cells (SECs) contribute to renal and pulmonary failure

Etiology- What is it?
Sinusoidal endothelial cells (SECs)

- SECs are permeable endothelial cells in the hepatic capillary system that act as a gateway between hepatic blood flow and the space of Disse where hepatocytes/hepatic stellate cells live (which regulate vasoconstriction and maintain hepatic venous pressure).

Vion, AC., et al., 2015

Microcirculation

Blood flows to central vein

Sinusoids

RBC

Additional pathways of injury

- Cytokines IL-1β, IL-6, IL-8, TNFα
- Intracellular adhesion molecule-1 (ICAM-1)
- Vascular adhesion molecule-1 (VCAM-1)
- Nitrous Oxide depletion
- PAI-1 (plasminogen activator inhibitor)
- Matrix Metalloproteinase activity


Embolization

Red blood cells embolized into Space of Disse

Sinusoidal endothelium injury

- Damage to SECs results in:
  - embolization of RBCs into the space of Disse
  - cellular destruction
  - obliteration of sinusoids

Glutathione:

A chemo-protectant produced in the liver.

Drugs that are metabolized by the cytochrome P450 pathway rely upon Glutathione to convert toxic metabolites into non-toxic variants.

Radiation, cyclophosphamide and busulfan deplete glutathione stores, rendering the hepatic sinusoids susceptible to damage.

CY is toxic to hepatocytes and SECs.

Eiseberg, S 2010

Sinusoidal endothelium injury

- Embolization of RBCs into the space of Disse
- Obliteration of sinusoids

Embolization

Red blood cells embolized into Space of Disse

Eisenberg, S 2010
Complete occlusion
After 14-21 days, sinusoids and venules are filled with collagen

General clinical features
- **Weight gain**: R/T fluid retention
- **Hepatomegaly**: R/T sinusoidal obstruction
- **Pain**: R/T stretching of liver capsule
- **Hyperbilirubinemia**: R/T inability of liver to clear broken down red cells
- **Ascites**: R/T decreased albumin production

Diagnostic procedures
- **Ultrasound**: Not useful in early disease
- **Hepatic Venous Gradient Pressure**: Wedge pressure >9-10mmHg is highly diagnostic
- **Transjugular liver biopsy**: Carries significant risk of hemorrhage

Lab tests
- **No specific lab test has been identified.**
- **Elevated bilirubin**:
  - Higher levels associated with increased mortality
  - Bilirubin not specific to HSOS (increased by TPN or cyclosporine toxicity, or infection)
  - Pediatric patients may not have elevated bilirubin
Lab tests

- Elevated ALT and AST
  - Sensitive hepatic markers but not specific to HSOS
- Elevated PAI-1 levels
  - Specific to HSOS
  - Not performed by most labs
  - Can also be elevated with sepsis
  - No agreed upon threshold for diagnosis

Differential Dx

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Also Seen With</th>
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<tbody>
<tr>
<td>Rapid weight gain</td>
<td>CHF, AKI</td>
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<tr>
<td>Hepatomegaly</td>
<td>CHF, Sepsis syndrome</td>
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<tr>
<td>Jaundice</td>
<td>Biliary infection, aGVHD</td>
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<th>Incidence</th>
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<td>3-60% (135 studies) but depends on “criteria” and age of study.</td>
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<tr>
<td>Using new EBMT criteria:</td>
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<td>10% adults</td>
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<tr>
<td>20% pediatrics</td>
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<td>Transplant type</td>
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Other possible risk factors

- Female gender
- GVHD prophylaxis using CSP/MTX and/or presence of GVHD
- Infusions of ABO incompatible platelets
Decreased Incidence

• Other differences from 1980s–2000:
  • fewer dose escalation studies
  • fewer active Hepatitis C patients
  • patients undergoing transplant sooner after diagnosis and are generally “healthier”
  • dosing busulfan by pharmacokinetics
  • increased use of IV Busulfan in place of oral

General

• Identify patients who are at risk for developing HSOS
  • Will help aid in targeting assessments and subsequent diagnosis
  • Accurately monitor patients with mild or early HSOS, as subtle changes can indicate worsening multi-organ functioning
  • Be prepared to assist with paracentesis

Hingorani, S. et al. 2017; Mahadeo, K. et al. 2017

Liver location

WHERE'S THE LIVER?

Hepatomegaly vs. Ascites

• Monitor renal and hepatic function (↑ uremia = ↑ bleeding potential)
• Measure abdominal girth QD or BID using unit standard
• Obtain QD or BID weights using unit standard
• Assess peripheral edema and elevate extremities

Wallhult, E. 2017; Murray, A. 2018
Jaundice/Hyperbilirubinemia

- Worn out red cells are broken down and release pigments biliverdin and bilirubin
- Bilirubin is insoluble in plasma unless bound to albumin, and accumulates in circulation if not conjugated by the liver.
- Jaundice occurs if bilirubin >2.5.
- Is not always present in pediatric patients

Myers, KC et al, 2015

Renal

- There is a delicate balance between hypovolemia and volume overload
  - Document accurate I&O
  - Monitor for volume overload

Murray, A. 2018

Hepatorenal Syndrome

- Related to hypovolemia (due to low albumin)
- Considered a be “pre-renal” condition
- Identified by a disproportionate BUN to Cr ratio (>1:10)

Example

<table>
<thead>
<tr>
<th>Condition</th>
<th>CR</th>
<th>BUN</th>
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<tbody>
<tr>
<td>Acute Tubular Necrosis</td>
<td>4.5</td>
<td>32</td>
</tr>
<tr>
<td>Hepatorenal Syndrome</td>
<td>4.5</td>
<td>96</td>
</tr>
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Murray, A. 2018; Soubani, AO., 2006; Stark, JL., 1994

Prevention strategies

- Regimen modification
  - Eliminating Cytoxan
  - Administering Cytoxan before Busulfan
  - Using IV Busulfan

Example

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| Prophylactic medications
  | Low Molecular Weight Heparin (LMWH)
  | Inconsistent study results
  | Ursodeoxycholic acid (UDCA) (Ursodiol)
  | Some benefits; only 2 studies
  | Only available as an oral agent
  | Defibrotide
  | Not FDA approved for prophylaxis
  | Expensive (median cost $198,000)

Carraras, E. 2014; Pichler, H. et al 2017;
Renal
• Avoid simultaneous infusions of nephrotoxic drugs
• Monitor electrolytes
• Collaborate with pharmacy to ensure sodium and fluid restriction and concentrate fluids when possible

(Ref: Hingorani, S. 2017; Mahadeo, K. et al. 2017)

Renal
• Monitor cyclosporine and tacrolimus levels
• Administer albumin if < 3gm/dL
• Administer diuretics judiciously to avoid hypovolemia and prevent worsening renal impairment

(Ref: Hingorani, S. 2017; Mahadeo, K. et al. 2017)

Cardiovascular
• Obtain orthostatic B/Ps
• Institute falls prevention protocol
• Perform hemodynamic monitoring as indicated
• Assess for possible pericardial effusions, cardiac tamponade
• Differentiate between esophagitis and cardiac-related chest pain

(Ref: Hingorani, S. 2017; Mahadeo, K. et al. 2017)

Respiratory
• Elevate HOB to ↑ lung expansion
• Assess for hypoventilation r/t hepatomegaly
• Assist with paracentesis to aid with lung expansion
• Measure O₂ saturation (will not show CO₂ retention)
• Auscultate lung sounds for presence of crackles

(Ref: Hingorani, S. 2017; Mahadeo, K. et al. 2017)

Integument
• Urea, bilirubin, and hypercalcemia cause pruritus
• Systemic medications
  - Diphenhydramine and hydroxyzine are usually ineffective
  - Chlorpheniramine and cypheptadine may be useful at night for their sedating effects but not itching
  - Claritin® and Zyrtec® may be useful
  - Ondansetron and aprepitant may be beneficial

(Ref: Pereira, MP, Kremer, AE, Mettang, & Stander, S., 2016; Chikotas, N. 2006; Bosonnet, L. 2003)

Integument
• Maintain cool environment to ↓ itching
• Educate patients to wear cotton, loose-fitting clothing
• Avoid use of soap to prevent dryness
• Use moisturizers for dry skin (e.g., Eurax, Sarna)
• Elevate edematous extremities to help control edema
• Protect against skin breakdown and maintain integrity

(Ref: Jakubowski, R. in Faiman’s BMT Certification Review Manual; Rentwert, J., 2016)
**Hematologic**

- Monitor PT/PTT and administer FFP
- Administer platelets (↑ risk of bleeding with ↑ bilirubin or BUN)
- Ensure patient safety and minimize potential for trauma

- Ford, R. et al. 1983

**Neurologic**

- Mental status changes can be from renal and/or hepatic failure
- Monitor for decreased LOC, confusion or agitation
- Administer narcotics and sedatives sparingly
- Perform pediatric screening q shift or per policy:
  - CAPD [Cornell Assessment of Pediatric Delirium]
  - pCAM-ICU [Pediatric Confusion Assessment Method for the Intensive Care Unit]
- Ensure patient safety

- Ovchinsky, N. et al. 2018

**Psychosocial**

- Be sensitive to altered body image issues related to jaundice, ascites, edema and anasarca
- Provide support and education to patient and family

- Ovchinsky, N. et al. 2018

**Treatment**

**Defibrotide**

- FDA approved 2017 for HSOS with renal or pulmonary dysfunction in adults and pediatrics
- Stimulates fibrinolysis by increasing endogenous tPA
- Anti-inflammatory and anti-thrombotic without intrinsic anticoagulant properties
  - Administered Q6 hours over 2 hours for a minimum of 21 days
  - Short half-life (2 hours)
  - Requires 0.2 micron filter
  - Response rates 35-60% (depending on study and population) and better responses seen with early initiation
  - Adding methylprednisolone ↑ survival rate to 75% in one pediatric study


- Defibrotide

- Bleeding is most common serious side effect; discontinue all medications that affect coagulation
- Other side effects include:
  - Hypotension
  - Gastrointestinal side effects (N,V,D)
  - Epistaxis
  - Hypersensitivity reactions (<2%)

- Defibelio Package Insert, 2016
Implications

- Patients with severe HSOS require almost twice the length of hospitalization, at nearly 3 times the overall cost.

Questions?