Hepatic Sinusoidal Obstruction Syndrome (HSOS)

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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

Modified Seattle Criteria 1984 (at least 2 of the following by day 20)
- Hepatomegaly with RUQ pain
- Jaundice
- Unexplained weight gain and/or ascites

Baltimore Criteria 1987 (Bilirubin ≥ 2 mg/dL and at least 2 of the following by day 21)
- Weight gain >5% from baseline
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EBMT Criteria for Adults 2016
- Classical (first 21 days)
- > 21 days
- Histologically proven HSOS or 2 or more of the following:
  - Weight gain >5% from baseline
  - Painful hepatomegaly
  - Bilirubin ≥ 2 mg/dL

Incidence
- 3-60% (135 studies) but depends on “criteria”
- Lower incidence than reported from 1980s-2000 due to:
  - Fewer dose escalation studies
  - Fewer Hepatitis C positive patients
  - Decrease in use of known hepatotoxic drugs
  - Patients undergoing transplant sooner after diagnosis and are “healthier”
  - Busulfan dosed by pharmacokinetics
  - (possibly) increased use of IV Busulfan in place of oral

Risk factors
- High-dose myeloablative chemotherapy
  - Regimens containing Busulfan (especially PO) + Cytoxan, or Methotrexate
- Prior transplant
- Allogeneic and matched unrelated
- Advanced disease at time of transplant
- DX of CML (adults) or osteopetrosis or Thalassemia (peds)
- Pre-existing liver disease
- Poor performance status (Karnofsky <90)
Possible risk factors

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

Sinusoidal endothelium injury

- Damage to sinusoidal endothelial cells (SECs) results in
  - embolization of RBCs
  - cellular destruction
  - obliteration of sinusoids

Additional pathways of injury

- Cytokines IL-6, IL-8, TNFα
- Nitrous Oxide depletion
- PAI-1 (plasminogen activator inhibitor)
- Matrix Metalloproteinase activity

Lobules and acini

- Lobules can be subdivided into functional units called "acini"
  - Acini are divided into 3 zones
  - Sinusoids allow flow of blood through acini
Diagnostic procedures

- Ultrasound
  - Not useful in early disease
  - May have value for differential diagnosis

- Hepatic Venous Gradient Pressure
  - Wedge pressure >9-10mmHg is highly diagnostic
  - Transjugular liver biopsy carries significant risk of hemorrhage

Lab tests

- 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

- Elevated ALT and AST
  - Sensitive hepatic markers but not specific to HSOS

- Elevated PAI-1 levels
  - Specific to HSOS, can also be elevated with sepsis


Assessment

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

Mohty, M. 2016

Hepatorenal Syndrome

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

<table>
<thead>
<tr>
<th>Example</th>
<th>Acute Tubular Necrosis</th>
<th>CR 4.5</th>
<th>BUN 32</th>
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<tbody>
<tr>
<td></td>
<td>Hepatorenal Syndrome</td>
<td>CR 4.5</td>
<td>BUN 96</td>
</tr>
</tbody>
</table>

Risk of mortality

- Depends on severity
- Severe HSOS results in MOF (multi-organ failure)
  - Develops in 20-40% of all allogeneic patients with HSOS
  - Mortality: >80% if untreated (MOF)

Richardson, P et al 2017
Prevention strategies

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

- Prophylactic medications
  - Low Molecular Weight Heparin (LMWH)
    - Inconsistent study results
  - Ursodeoxycholic acid (UDCA) (Ursodiol)
    - Some benefit; only 2 studies
    - Only available as an oral agent
  - Defibrotide
    - Not FDA approved for prophylaxis
    - Expensive

Treatment

- Defibrotide
  - FDA approved 2017 for HSOS with renal or pulmonary dysfunction in adults and peds
  - 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
  - Requires 0.2micron filter


Defibrotide

- Bleeding is most common serious side effect
- Other side effects include:
  - Hypotension
  - Gastrointestinal
  - Hypersensitivity reactions (<2%)
- Response rates 35-60% (depending on study and population) and better responses seen with early initiation
- Adding methylprednisolone ↑ survival rate to 73% in one pediatric study

Gloude, N. et al 2018

Nursing interventions
Renal
- Monitor renal and hepatic function \[\text{uremia} = \uparrow \text{bleeding potential}\]
- Measure abdominal girth QD or BID
- Document accurate I&O
- Concentrate IV volumes
- Assess peripheral edema and elevate extremities
- Place on sodium and fluid restriction and monitor electrolytes
- Avoid simultaneous infusions of nephrotoxic drugs

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

Renal
- Monitor cyclosporine and tacrolimus levels
- Administer albumin if < 3gm/dL
- Administer diuretics judiciously
  - Avoid hypovolemia

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

Cardiovascular
- Orthostatic B/Ps
- QD or BID weights
- Hemodynamic monitoring as indicated
- Assess for possible pericardial effusions, cardiac tamponade
- Rule out esophagitis

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

Respiratory
- Elevate HOB
- Assess for hypoventilation
- Assist with paracentesis to aid with lung expansion
- Measure \(O_2\) saturation (will not show \(CO_2\) retention)
- Auscultate lung sounds for presence of crackles

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Integument
- Maintain skin integrity
- Avoid use of soap
- Use moisturizers for dry skin (e.g., Eurax, Sarna)
- Elevate edematous extremities
- Maintain cool environment
- Cotton, loose-fitting clothing
- Protect against breakdown

Integument
- Urea and bilirubin cause pruritis
  - Systemic medications
    - Diphenhydramine and hydroxyzine are usually ineffective
    - Chlorpheniramine and cyproheptadine may be useful at night due to sedating effects
    - Claritin®, Zyrtec® may be useful
    - Ondansetron may be beneficial
Hematologic
- Monitor PT/PTT and administer FFP
- Administer platelets (↑ risk of bleeding with ↑ bilirubin or BUN)
- Ensure patient safety and minimize potential for trauma

Neurologic
- Mental status changes can be from renal and/or hepatic failure
- Monitor for decreased LOC, confusion or agitation
- Administer narcotics and sedatives sparingly
  - Peds: avoid benzodiazepines; use dexmedetomidine instead
- Perform pediatric screening (CAPD or pCAM-ICU) q shift
- Ensure patient safety

Psychosocial
- Be sensitive to altered body image issues
- Provide support and education to patient and family