Veno-Occlusive Disease (VOD)  
AKA Hepatic Sinusoidal Obstruction Syndrome (SOS)

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Disclosures

• No financial disclosures
• No discussion of off-label use of medication
Roadmap

• Pathophysiology
• Risk factors
• Clinical presentation
• Diagnosis
• Treatment
• Critical care management
• Summary
PATHOPHYSIOLOGY
Injury to the hepatic venous endothelium (sinusoidal endothelial cells and zone 3 hepatocytes) – conditioning chemotherapy, gemtuzumab/inotuzumab, radiation (>30 Gy)
Activation of endothelial cells →
↑thrombosis, ↓fibrinolysis, ↑inflammation, ↓cytoskeletal structure →
Narrowing of sinusoids
Increased thrombosis and decreased thrombolysis $\rightarrow$ VOD/SOS
RISK FACTORS
## Risk Factors

<table>
<thead>
<tr>
<th>Patient-Related Factors</th>
<th>OR</th>
<th>Transplantation-Related Factors</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age [5,24]</td>
<td>1.7-9.5</td>
<td>Allogeneic HSCT [24]</td>
<td>2.8</td>
</tr>
<tr>
<td>Preexisting hepatic condition</td>
<td>3.4</td>
<td>Unrelated/HLA mismatch [24]</td>
<td>1.4</td>
</tr>
<tr>
<td>Previous liver disease [24]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated AST/ALT pre-HCST [24]</td>
<td>2.4-4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C-positive [26]</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying diagnosis</td>
<td></td>
<td>Previous HSCT [24]</td>
<td>1.9</td>
</tr>
<tr>
<td>Leukemia [24]</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td>High-intensity/MAC regimens</td>
<td>2.3-7.9</td>
</tr>
<tr>
<td>Inotuzumab ozogamicin [6],*</td>
<td>22</td>
<td>Fludarabine [24]</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBI-based [26]</td>
<td>1.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Busulfan-based [26,30]</td>
<td>2.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Busulfan-thiotepa [36]</td>
<td>8.8</td>
</tr>
<tr>
<td>Previous abdominal radiation [24]</td>
<td>2.9</td>
<td>Total body irradiation [24]</td>
<td></td>
</tr>
<tr>
<td>Impaired pulmonary function [24]</td>
<td>2.4</td>
<td>&gt;12 Gy plus cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td>Genetic predisposition [24]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTM1 null genotype</td>
<td>4.1</td>
<td>Sirolimus + methotrexate + tacrolimus</td>
<td>3</td>
</tr>
<tr>
<td>KPS score &lt;90% [24]</td>
<td>2.7</td>
<td>Methotrexate + cyclosporine</td>
<td>3.3</td>
</tr>
<tr>
<td>Ferritin &gt;1000 ng/mL pre-HSCT [24]</td>
<td>3.1</td>
<td>Cyclosporine</td>
<td>4.2</td>
</tr>
<tr>
<td>Ferritin &gt;950 ng/mL pre-HSCT [36]</td>
<td>8.8</td>
<td>Horse ATG [37]</td>
<td>3.5</td>
</tr>
<tr>
<td>Sepsis post-HSCT [24]</td>
<td>4.1</td>
<td>Trough serum tacrolimus levels above target range (5-10 ng/mL) [21]</td>
<td>1.4</td>
</tr>
<tr>
<td>ECOG performance status 2-4 (vs 0-1) [26]</td>
<td>1.9</td>
<td>Early day of neutrophil engraftment [5]</td>
<td></td>
</tr>
<tr>
<td>Advanced disease status [26]</td>
<td>1.5-1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury [21]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet refractoriness [21]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High INR [21]</td>
<td></td>
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</tbody>
</table>

Risk Factors

- Pediatric patients have a 2- to 3-fold higher incidence than adults, estimated at 20-30%
  - Infants 30% (as high as 60%)
  - Osteopetrosis 60%
  - Neuroblastoma 30%
  - Macrophage activating syndromes 30%
  - Thalassemia 30%

CLINICAL PRESENTATION
Clinical Presentation

Time to VOD/SOS occurrence (days)

Median time to VOD/SOS = 17 days (range, 1-104)
Interquartile range = 11 days
90th percentile = 29 days

Figure 2. Time to VOD/SOS occurrence (days).

Clinical Presentation

• Weight gain (fluid retention) – first
• Can see thrombocytopenia and platelet refractoriness
• Hyperbilirubinemia/jaundice, transaminitis
  – Anicteric in ~30% of pediatric patients
• Firm, painful hepatomegaly with ascites
• Renal insufficiency (hepatorenal syndrome) in 50%
  – Need for dialysis in 25%
• Multiorgan failure, hepatic encephalopathy, death

Corbacioglu et al. Lancet 2012
Naples et al. Blood 2014
Myers et al. BBMT 2015
Imaging

• Ultrasound findings:
  – Reversal of flow in the portal vein (sensitivity low)
  – Ascites
  – Thickening of gall bladder wall
  – Hepatic artery resistance index >0.75
Pathology

• Gold standard, but rarely performed
  – Transjugular > percutaneous
• Liver sinusoids dilated and congested
• Fibrous occlusion of central veins and small venules
• Zonal liver disruption
• Centrilobular hemorrhagic necrosis
• Later:
  – Collagen deposition in sinusoids
  – Sclerosis of venular walls
  – Fibrosis of venular lumens
  – Occlusion of terminal hepatic venules
DIAGNOSIS
Diagnosis

• **Modified Seattle Criteria**: 2+ of the following within 20 days of HCT
  – Total bilirubin > 2 mg/dL
  – Hepatomegaly or RUQ pain
  – Sudden weight gain due to fluid accumulation (>2% of baseline)

• **Baltimore criteria**: Bilirubin > 2mg/dL within 21 days of HCT plus at least 2 of the following:
  – Hepatomegaly
  – Ascites
  – Weight gain >5% from baseline
Diagnosis

• Problems with the Modified Seattle and Baltimore criteria
  – Time frame (>20-21 days in 25-30%)
  – Weight fluctuation in children
  – Anicteric presentation in 30%

SPECIAL REPORT

Diagnosis and severity criteria for sinusoidal obstruction syndrome/veno-occlusive disease in pediatric patients: a new classification from the European society for blood and marrow transplantation


Table 2. EBMT diagnostic criteria for hepatic SOS/VOD in children

- No limitation for time of onset of SOS/VOD

The presence of two or more of the following:

- Unexplained consumptive and transfusion-refractory thrombocytopenia
- Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain > 5% above baseline value
- Hepatomegaly (best if confirmed by imaging) above baseline value
- Ascites (best if confirmed by imaging) above baseline value
- Rising bilirubin from a baseline value on 3 consecutive days or bilirubin ≥ 2 mg/dL within 72 h

Abbreviations: CT = computed tomography; HCT = hematopoietic cell transplantation; MRI = magnetic resonance imaging; SOS/VOD = sinusoidal obstruction syndrome/veno-occlusive disease; US = ultrasonography. aWith the exclusion of other potential differential diagnoses. b ≥ 1 weight-adjusted platelet substitution/day to maintain institutional transfusion guidelines. cSuggested: imaging (US, CT or MRI) immediately before HCT to determine baseline value for both hepatomegaly and ascites.
### EBMT Severity

<table>
<thead>
<tr>
<th>CTCAE</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe MOD/MOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LFT&lt;sup&gt;b&lt;/sup&gt; (ALT, AST, GLDH)</td>
<td>( \leq 2 \times \text{normal} )</td>
<td>&gt; 2 and ( \leq 5 \times \text{normal} )</td>
<td>&gt; 5</td>
<td></td>
</tr>
<tr>
<td>Persistent RT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 3 days</td>
<td>3–7 days</td>
<td>&gt; 7 days</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)&lt;sup&gt;b, c&lt;/sup&gt;</td>
<td>&lt; 2</td>
<td>&gt; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (( \mu \text{mol/L} ))</td>
<td>&lt; 34</td>
<td></td>
<td>&gt; 34</td>
<td></td>
</tr>
<tr>
<td>Ascites&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Necessity for paracentesis (external drainage)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin kinetics</td>
<td></td>
<td></td>
<td>Doubling within 48 h</td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired coagulation</td>
<td>Impaired coagulation with need for replacement of coagulation factors</td>
</tr>
<tr>
<td>Renal function GFR (mL/min)</td>
<td>89–60</td>
<td>59–30</td>
<td>29–15</td>
<td>&lt; 15 (renal failure)</td>
</tr>
<tr>
<td>Pulmonary function (oxygen requirement)</td>
<td>&lt; 2 L/min</td>
<td>&gt; 2 L/min</td>
<td>Invasive pulmonary ventilation (including CPAP)</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>New onset cognitive impairment</td>
</tr>
</tbody>
</table>

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*Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CNS = central nervous system; CPAP = continuous positive airway pressure; CTCAE = Common Terminology Criteria for Adverse Events; GFR = glomerular filtration rate; GLDH = glutamate dehydrogenase; LFT = liver function test; MOD/MOF = multi-organ dysfunction/multi-organ failure; RT = refractory thrombocytopenia; SOS/VOD, sinusoidal obstruction syndrome/veno-occlusive disease. If patient fulfills criteria in different categories they must be classified in the most severe category. In addition, the kinetics of the evolution of cumulative symptoms within 48 h predicts severe disease. Presence of \( \geq 2 \) of these criteria qualifies for an upgrade to CTCAE level 4 (very severe SOS/VOD). Excluding pre-existing hyperbilirubinemia due to primary disease.*
EBMT Criteria

• Goal of earlier diagnosis → earlier treatment
• Evidence to suggest earlier treatment associated with improved outcomes
  – Reduced use of platelets, hospitalization, ICU admission
  – Less transplant-related morbidity and mortality

Early Treatment with Defibrotide

<table>
<thead>
<tr>
<th>N=45</th>
<th>≤2 Days</th>
<th>&gt;2 Days</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>94%</td>
<td>30%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Complete Response in Pts with severe VOD</td>
<td>83%</td>
<td>10%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Corbacioglu et al, BMT 2004
Differential Diagnosis

• Budd-Chiari syndrome
  – Obstruction of hepatic veins or IVC rather than hepatic venules and sinusoids

• Acute GVHD
  – Usually has concurrent skin and/or GI involvement

• Hepatic infections
  – CMV, VZV, EBV, HHV6, adenovirus, candidiasis

• Drug toxicity
  – Calcineurin inhibitors (cyclosporine, tacrolimus), MTX, azoles, Bactrim, ribavirin, busulfan
TREATMENT
Prevention

- Risk reduction
  - Avoidance of hepatotoxic medications
  - Iron chelation for iron overload
  - Preparative regimen choice
  - GVHD prophylaxis choice

- Prophylaxis
  - Ursodiol
  - High-risk children – defibrotide
    - Lower incidence of VOD 12 vs 20%
    - Lower incidence of renal failure 1 vs 6%
    - Mortality at 100 and 180 days similar
    - No increase in hemorrhage

Corbacioglu et al. Lancet 2012
Treatment

• **Supportive care**
  – Fluid management
  – Paracentesis
  – Dialysis
  – Respiratory support
  – Pain control
  – Minimize hepatotoxic agents

• **Defibrotide**
  – 23% improvement in survival at Day +100 versus control ($P=0.0109$)
  – 19% improvement in CR rate at Day +100 versus control ($P=0.0160$)

Treatment

- Day +100 survival rate of 73% and an overall VOD complete resolution rate of 66.7%, higher than the rates reported in the recent literature using defibrotide alone (40% to 50% day +100 overall survival)

- RCT needed
CRITICAL CARE MANAGEMENT

Some notes courtesy of Jennifer McArthur, DO
Importance of Active Vigilance

• **Accurate I/Os** (Q2H) and **weights** (2-3x/day)
  – First sign of VOD usually weight change
  – Capillary leak syndrome

• Monitoring for right upper quadrant pain and abdominal distension (ascites)

• Observation for bleeding

• Blood product support

• Trending labs (ie platelet refractoriness and bilirubin)
Renal Dysfunction

• Multifactorial
  – Hepatorenal syndrome (50%)
    • Dialysis needed in 25%
  – Endothelial dysfunction
  – Nephrotoxins (i.e., vancomycin, tacrolimus, acyclovir)
  – Poor perfusion
    • Third spacing
    • Increased intra-abdominal pressure
    • Altered cardiac output

• Avoid acute fluid overload if possible
  – Fluid restriction, maximally concentrate medications/TPN
  – Diuresis
Fluids, Electrolytes, Renal Dysfunction

Patient diagnosed with VOD and weight gain / FO > 2.5%

Monitoring Guidelines
- Strict I+O per nursing shift
- Twice daily weights
- Monitor electrolytes every 8h until stable
- Rising BUN/Cr is expected
- Close hemodynamic monitoring
- Maintain serum albumin >3gm/dl
- Monitor for ACS

Fluid Restriction & Diuresis
- Fluid restriction to 75-50% normal fluid intake
- Furosemide prn
- Increase furosemide 0.5 to 1 mg/kg/dose q6-12h
- Increase to continuous furosemide infusion prn

Adjunctive Therapy
- Medications: Chlorothiazide, Bumetanide, Metolazone, Spironolactone
- Address ACS if present by paracentesis

Worsening wt gain and FO despite medical management
- FO ≥ 10% -15% despite medical management
- Electrolyte abnormalities despite medical management
- Progressive oliguria/anuria

Renal Replacement Therapy
- Maintain platelet >50,000
- High sepsis vigilance
- Care coordination among specialty teams

Mahadeo et al. BBMT (2017).
Cardiac

• Fluid overload/3rd spacing
  – HR and BP monitoring
  – CVP – measures volume status and cardiac function
    • Normal = 6 – 10 (too high – FO/stiff ventricle, too low – dehydration, capillary leak, bleeding)
  – MVO\textsubscript{2} – mixed venous oxygen saturation – marker of cellular oxygen uptake

• Hypotension and hypertension
  – Fluid shifts
  – Kidneys may need higher MAP with increased intra-abdominal pressures

• Pulmonary hypertension (pulmonary VOD)
Blood Pressure

• **Organ perfusion pressure** = MAP - CVP (goal >50-60)
  – May need higher with increased abdominal pressure to perfuse kidneys
  – Need higher with chronic hypertension (organs used to it)

• **Cerebral Perfusion Pressure** = MAP - ICP (goal >60 cm H\(_2\)O)

• **Pulse Pressure** = SBP - DBP
  – Narrowing in impending cardiac tamponade
  – Wide in warm sepsis/cytokine release
Respiratory

• Causes of respiratory failure
  – Over-sedation
  – Fluid overload → pleural effusions
  – Increased abdominal pressure
  – Intrinsic pulmonary disease (engraftment, pulmonary GVHD, infection, pulmonary VOD)

• Respiratory Failure Management
  – Non-invasive ventilation vs invasive mechanical ventilation
    • NIV relatively contraindicated with significant abdominal distension
    • IMV requires increased sedation; more delirium; deconditioning
      – Indicated in NIV failure, severe hypoxia, AMS, upper airway obstruction
  – Tight control of fluid balance
  – Paracentesis vs thoracentesis
    • Paracentesis easier, less pain, can help with both compartments

Ovchinsky et al. BBMT (2018).
Intra-Abdominal Hypertension

- Can impede diaphragm excursion
- Reduces renal perfusion
- Reduces bowel perfusion
- Management
  - NG to LIS
  - Foley
  - Treat constipation
  - Muscle relaxants
  - Paracentesis
Ascites and Pleural Effusions

- Paracentesis if ascites does not respond to medical management (intraabdominal hypertension, compartment syndrome, or hypoxia)
  - Continuous pump-controlled drainage preferred over manual, open drainage to gravity discouraged
  - Albumin can be used to prevent hypoalbuminemia after paracentesis
  - Once drainage <5 ml/kg/day, catheter should be clamped for 24 hours and then may be removed
- Thoracentesis if fluid contributing to pulmonary dysfunction
  - Once drainage <3 ml/kg/day should be clamped for 24 hours and then removed if no significant re-accumulation or respiratory compromise

Figure 2. Flowsheet showing management of ascites and respiratory and renal dysfunctions. ACS, abdominal compartment syndrome; IAH, intra-abdominal hypertension; AKI, acute kidney injury; FO, fluid overload.

Mahadeo et al. BBMT (2017).
## Transfusion Support and Coagulopathy Management

### Table 3
Summary Recommendations for Transfusion and Coagulopathy Issues in Patients with Veno-Occlusive Disease

<table>
<thead>
<tr>
<th>Question</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q.14</td>
<td>The recommended transfusion threshold is a platelet count of $20 \times 10^9/L$ for patients not on thrombolytic therapy and $30 \times 10^9/L$ for patients on thrombolytic therapy.</td>
</tr>
<tr>
<td>Q.15</td>
<td>Low-dose platelets should be transfused in patients with veno-occlusive disease (VOD).*</td>
</tr>
<tr>
<td>Q.16</td>
<td>Platelets should be infused over 30 minutes unless there are volume-related issues due to small patient size. The infusions should be given as needed to meet the platelet threshold.</td>
</tr>
<tr>
<td>Q.17</td>
<td>ABO-identical platelets should be transfused in all patients.</td>
</tr>
<tr>
<td>Q.18</td>
<td>Thromboelastography and rotational thromboelastography monitoring (if available) should be considered as an adjunctive tool to help guide transfusion of frozen plasma, cryoprecipitate, and platelets.</td>
</tr>
<tr>
<td>Q.19</td>
<td>Fresh frozen plasma and cryoprecipitate are recommended for treatment of bleeding patients with abnormal routine coagulation testing (RCT), but not for correction of RCT abnormalities in a non-bleeding patient.</td>
</tr>
<tr>
<td>Q.20</td>
<td>Patients should be given blood transfusion when the hemoglobin level falls below 7 g/dL.</td>
</tr>
<tr>
<td>Q.21</td>
<td>Treatment for acute bleeding includes blood product transfusions, alleviating coagulation dysfunctions to achieve hemostasis, and discontinuing all offending medications. Recombinant activated factor VII can be used in life-threatening situations.</td>
</tr>
</tbody>
</table>

Neurologic Dysfunction

• **Hepatic encephalopathy**
  – Rifaximin > lactulose
  – Invasive intracranial monitoring for ICH not routinely recommended
  – Transcranial Doppler may be used
  – Prophylactic induction of hypernatremia (Na 145-155 mEq/L) recommended in advanced encephalopathy and evidence of cerebral edema
  – ICH → mannitol bolus (0.5-1.0 g/kg) first line

• **Delirium**
  – Routine screening each nursing shift
    • Cornell Assessment of Pediatric Delirium (CAPD)
    • Pediatric Confusion Assessment Method (PCAM) for ICU screening
  – Nonpharmacologic approach first
    • Minimize risk factors
    • Early mobilization
  – Refractory → Atypical antipsychotics
  – Avoid sedation if possible, but if needed, dexmedetomidine > benzodiazepines
Summary

• Vigilance for signs/symptoms of VOD paramount to early diagnosis (EBMT criteria)
• Early diagnosis → early treatment with defibrotide → better outcomes
• Aggressive management of fluid overload important
• Despite this, many will go into multi-organ dysfunction/failure → ICU management of renal, cardiac, pulmonary, GI, coagulation, neurologic dysfunction
THANK YOU!

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