TMA and BK Virus in HSCT: What the nephrologist and oncologist should know

Benjamin Laskin, MD, MS
Associate Professor
Division of Nephrology
The Children’s Hospital of Philadelphia
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Bio

- Benjamin Laskin, MD, is Chief of the Division of Nephrology and an attending physician at the Children’s Hospital of Philadelphia. Dr. Laskin is also an Associate Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

- Dr. Laskin completed his undergraduate at Duke University where he graduated with a major in Economics. He attended the University of Maryland School of Medicine and completed his pediatrics residency and fellowship in pediatric nephrology at Cincinnati Children’s Hospital Medical Center.

- Following his fellowship, he joined the faculty at the Children’s Hospital of Philadelphia. Dr. Laskin’s research interests are in infections and kidney disease in immunosuppressed children, including those receiving a bone marrow or solid organ transplant. He was the recipient of a K23 Career Development Award from the National Institutes of Health and currently is PI of an R01 designed to study viral and host predictors of hemorrhagic cystitis after bone marrow transplant. He serves as the Operations Director for the Transplant Center at Children's Hospital of Philadelphia.
Objectives

• Understand risk factors for thrombotic microangiopathy (TMA) after hematopoietic cell transplant

• Introduce strategies to diagnose and manage TMA after hematopoietic cell transplant

• Review BK polyomavirus as a potential trigger for TMA
Disclosures

• Dr. Laskin and this work were/are supported by K23 DK101600 and R01 DK125418

• Viracor-Eurofins tested the samples for BK virus at no charge

Mechanism/Location of Injury

Calcineurin inhibitors
Nephrotic syndrome
GVHD
Medication/chemotherapy/antimicrobial-related

TMA
Viral nephropathy
Glomerulus
Bowmans capsule
Proximal tubule
Loop of Henle
Distal tubule
Collecting duct
Obstruction/hemorrhagic cystitis
Thrombotic microangiopathy (TMA)

Endothelial cells separated from basal membrane and floating inside the vessel lumen

Red cell extravasation into tissues

TMA markers

- Red Cell
- Haptoglobin
- Free Hemoglobin
- LDH (Lactate dehydrogenase)
- Schistocyte
- Clumped platelets
- Injured vessel wall
<table>
<thead>
<tr>
<th>TMA INCIDENCE</th>
<th>Children</th>
<th>Adults</th>
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</thead>
<tbody>
<tr>
<td>Allo-HSCT</td>
<td>20-30%</td>
<td>15-20%</td>
</tr>
<tr>
<td>Auto-HSCT</td>
<td>10%</td>
<td>Not well studied</td>
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</tbody>
</table>

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<tr>
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<tbody>
<tr>
<td>Schistocytes</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Elevated LDH</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Thrombocytopenia</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Decreased hemoglobin</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Negative Coombs test</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Increased serum creatinine</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Decreased haptoglobin</td>
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<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Elevated soluble C5b-9</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Proteinuria</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Hypertension</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
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<tr>
<td>Other</td>
<td>Neurologic dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TA-TMA Index ≥ 20</td>
</tr>
</tbody>
</table>

LDH Lactate dehydrogenase, HSCT-TMA Hematopoietic stem cell transplantation-associated thrombotic microangiopathy, TA-TMA Transplant-associated thrombotic microangiopathy

Early insights into potential mechanisms of injury

Donor Specific Antibody (DSA) in AMR after kidney tx

“Recipient Specific Antibody” (RSA) in TMA after HCT?

- Is this why patients get so hypertensive?
- Is this why rituximab has been reported to work in some patients?

Laskin et al, Transplantation. 2013
Proteinuria and elevated sC5b-9 are poor prognostic markers at TMA diagnosis

Very high risk patient group (10 in 100 transplants)

Jodele et al. Blood. 2014 May 29
Complement dysregulation and TMA outcomes

• Complement blockade may improve TMA outcomes
  – pediatric experience is using C5 blocker eculizumab
  – adult experience using MASP2 inhibitor narsoplimab

• High risk TA-TMA treated with eculizumab (n=64):
  – Subjects with higher sC5b-9 at TA-TMA diagnosis less likely to respond to eculizumab and/or required more eculizumab doses

Genetic predisposition?

### Clinical Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/m Mechanism of action</th>
<th>Class</th>
<th>Company</th>
<th>Status</th>
<th>ClinicalTrials.gov</th>
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</thead>
<tbody>
<tr>
<td>Eculizumab</td>
<td>C5 inhibition</td>
<td>mAb</td>
<td>Alexion Pharmaceuticals</td>
<td>Phase 2 ongoing; off-label use in clinic (adult) [162]</td>
<td>NCT03518203 (adult) [162]</td>
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<tr>
<td>Ravulizumab (ALXN1210)</td>
<td>C5 inhibition</td>
<td>mAb</td>
<td>Alexion Pharmaceuticals</td>
<td>Phase 3 ongoing</td>
<td>NCT04543591 (adult) [141] NCT04557735 (adult) [142]</td>
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<tr>
<td>Nomacopan (Coversin)</td>
<td>C5 and LTb4 inhibition</td>
<td>Recombinant protein</td>
<td>Akari Therapeutics</td>
<td>Phase 3 ongoing</td>
<td>NCT04784455 (adult)[145]</td>
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<tr>
<td>Narsoplimab (OMS721)</td>
<td>MASP-2 Inhibition</td>
<td>mAb</td>
<td>Omeros Corporation</td>
<td>Phase 2 complete</td>
<td>NCT02222545 (adult)[147]</td>
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</tbody>
</table>


Novel biomarkers/pathways

Viral trigger?

Renal biopsy in patient with BK infection and TA-TMA:
BK virus in situ hybridization demonstrated positive staining in the glomerulus and Bowman’s capsule

Immunofluorescence microscopy of circulating endothelial cells from patient with BKPyV viremia. Polyomavirus (VP-1, green), endothelial (UEA-1, red) and nuclear (DAPI, blue) markers.

BK virus

• BK virus, similar to other DNA viruses (CMV, EBV), establishes a latent state after primary infection

• BK virus infects about 90% of the general population by 10 years of age and then remains dormant in the urothelial cells of the kidney and bladder

• Clinical disease is almost exclusively limited to patients receiving immunosuppression
  – Hemorrhagic cystitis after HCT
  – Nephropathy after kidney transplant
BK virus after kidney transplant

BK virus after kidney transplant

**Decoy Cells**

**Nephropathy**

**LTA staining**

<table>
<thead>
<tr>
<th></th>
<th>To detect biopsy-proven BK virus nephropathy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sens</td>
</tr>
<tr>
<td>Decoy cells in urine</td>
<td>100%</td>
</tr>
<tr>
<td>Viremia</td>
<td>100%</td>
</tr>
</tbody>
</table>

All subjects with nephropathy had BK viremia: \(\geq 7700\) copies/mL

Is the 10,000 cutoff valid across centers?

BK virus exists as 4 genotypes with geographic and evolutionary variation!

Kidney transplant case report:

National reference laboratory showed a BKV load <325 copies/mL

Testing at the treating institution had BKV loads of 46,000-86,000 copies/mL

Patient had biopsy-proven nephropathy

The patient was infected with BKV genotype IV


Clinical evidence for BK and TMA

• 1070 blood samples from 193 subjects
• 97% were negative for viremia pre-HCT
• In the first 3 months, 19% had peak viremia ≥10,000 copies/mL

<table>
<thead>
<tr>
<th>Peak Viremia in first 3 month</th>
<th>&lt;10,000 copies/mL</th>
<th>≥10,000 copies/mL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD grade ≥2</td>
<td>26%</td>
<td>47%</td>
<td>0.02</td>
</tr>
<tr>
<td>TMA</td>
<td>35%</td>
<td>79%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>34%</td>
<td>35%</td>
<td>0.84</td>
</tr>
<tr>
<td>Received dialysis</td>
<td>3%</td>
<td>18%</td>
<td>0.006</td>
</tr>
<tr>
<td>Overall survival at 1 year</td>
<td>88%</td>
<td>70%</td>
<td>0.001</td>
</tr>
</tbody>
</table>
BK virus management

• Check for BK in the urine in patients with cystitis
• Check for BK in the blood in patients with unexplained chronic increases in serum creatinine, consider biopsy
• Lower immunosuppression when able
• IVIG/leflunomide/cidofovir?
• Virus specific T cell infusions?
Thanks for your attention and happy to answer any questions