Thrombotic Microangiopathy in Kidney Transplantation

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Disclosures & Conflict of Interest

- I serve on the Scientific Advisory Board of Alexion Pharmaceuticals.
Objectives

• Describe the basic pathophysiology of Thrombotic Microangiopathies.
• Describe the most important causes of thrombotic microangiopathies in the context of kidney transplantation.
• Describe management strategies for the treatment of TTP and Atypical HUS.
• Describe other important causes of immediate post-transplant hemolysis.
Case 1

- 15 month old WM with 1 month history of URI treated with multiple antibiotics presented to MCV 7/30/87 with fever to 102, bruising and oliguria
- **PE:** BP: 136/87
- Pallor
- Petechiae
- Purpura
- **Labs of note:**
  - BUN/creatinine 44/1.0
  - Hgb 7, Plts 70K
  - Schistocytes on smear
Case 1

- Rx: Plasma infusion
- Worsening oliguria, edema, hypertension, renal failure
- PD started on 8-15-87
- LRD renal transplant from his mother 5-25-88
- Maintained on Prednisone and Azathioprine
- Creat stable at 0.6
- Presented to clinic on 4/24/89 with BUN 83, creat 2.6, Hgb 9.4, Plts 69K
PAS Stain of Renal Allograft
Case 1

- Deceased donor kidney transplant on 7/13/99
- Positive Flowcytometric crossmatch
- Rx induction thymoglobulin, PP for 13 sessions, tacrolimus, steroids and Cytoxan
- Excellent urine output and prompt renal function with POD 5 creatinine 1.1
- Creatinine rose to 2.9 and BUN 102 with plt count of 56K
- Failed in 2001 despite multiple therapies.
Case 1

- Interested in re-transplantation
- Issues of concern:
  - Cause of his TMA?
  - Risk of recurrence?
  - Can you prevent recurrence?
Case 2

• 48yoWF:
  • Multiple strokes in 1998.
  • Evidence of hemolysis (low platelets, hemoglobin, schistocytes on smear).
  • Treated with 3 sessions of plasma exchange -> complete recovery.
  • Diagnosed with heterozygous Factor V Leiden mutation which was presumed to be the cause of her initial presentation and maintained on warfarin.
  • Several years after her initial presentation she developed progressive chronic kidney disease presumed secondary to hypertension.
Case 2

• LURT Feb 2015 at VCUHS.
• On post-op Day 2
  • Platelets 60K (from>200K).
  • Hb 7.1 (from 9.6).
  • Schistocytes on smear.
  • Undetectable haptoglobin and high LDH
  • Decline in urine output->taken to OR for ? hematoma->No abnormalities.
Case 2

• Issues of concern:
  • Cause of her TMA?
  • How do you treat it acutely?
  • Can you prevent relapse?
Thrombotic Microangiopathy

A TMA is defined by:

- **Thrombocytopenia**
  - Platelet count <150,000 or >25% decrease from baseline

- **Microangiopathic hemolysis**
  - Schistocytes and/or Elevated LDH and/or Decreased haptoglobin and/or Decreased hemoglobin

Plus 1 or more of the following:

- **Neurological symptoms**
  - Confusion and/or Seizures and/or Other cerebral abnormalities

- **Renal impairment**
  - Elevated creatinine and/or Decreased eGFR and/or Elevated blood pressure and/or Abnormal urinalysis

- **Gastrointestinal symptoms**
  - Diarrhea ± blood and/or Nausea/vomiting and/or Abdominal pain and/or Gastroenteritis
# Primary TMA Syndromes

<table>
<thead>
<tr>
<th>Name</th>
<th>Cause</th>
<th>Clinical Features</th>
<th>Initial Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary disorders</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ADAMTS13 deficiency-mediated TMA (also called TTP)</td>
<td>Homozygous or compound heterozygous ADAMTS13 mutations</td>
<td>Initial presentation is typically in children but may also be in adults; possible evidence of ischemic organ injury; acute kidney injury is uncommon; patients with heterozygous mutations are asymptomatic.</td>
<td>Plasma infusion</td>
</tr>
<tr>
<td>Complement-mediated TMA</td>
<td>Mutations in CFH, CFI, CFB, C3, CD46, and other complement genes causing uncontrolled activation of the alternative pathway of complement</td>
<td>Initial presentation is often in children but may also be in adults; acute kidney injury is common; patients with heterozygous mutations may be asymptomatic.</td>
<td>Plasma infusion or exchange, anti-complement agent</td>
</tr>
<tr>
<td>Metabolism-mediated TMA</td>
<td>Homozygous mutations in MMACHC (encoding methylmalonic aciduria and homocystinuria type C protein)</td>
<td>Initial presentation is typically in children &lt;1 year of age; also reported in one young adult with hypertension and acute kidney injury.</td>
<td>Vitamin B₁₂, betaine, folinic acid</td>
</tr>
<tr>
<td>Coagulation-mediated TMA</td>
<td>Homozygous mutations in DGKE; mutations in PLG and THBD also implicated</td>
<td>Initial presentation with acute kidney injury is typically in children &lt;1 year of age with DGKE mutations; clinical features of disorders associated with other mutations have not been described.</td>
<td>Plasma infusion</td>
</tr>
<tr>
<td><strong>Acquired disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAMTS13 deficiency-mediated TMA (also called TTP)</td>
<td>Autoantibody inhibition of ADAMTS13 activity</td>
<td>Initial presentation is uncommon in children; often presents with evidence of ischemic organ injury; acute kidney injury is uncommon.</td>
<td>Plasma exchange, immunosuppression</td>
</tr>
<tr>
<td>Shiga toxin-mediated TMA (also called ST-HUS)</td>
<td>Enteric infection with a Shiga toxin-secreting strain of Escherichia coli or Shigella dysenteriae</td>
<td>Initial presentation is more common in young children, typically with acute kidney injury; most cases are sporadic; large outbreaks also occur.</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Drug-mediated TMA (immune reaction)</td>
<td>Quinine and possibly other drugs, with multiple cells affected by drug-dependent antibodies</td>
<td>Initial presentation is a sudden onset of severe systemic symptoms with anuric acute kidney injury.</td>
<td>Removal of drug, supportive care</td>
</tr>
<tr>
<td>Drug-mediated TMA (toxic dose-related reaction)</td>
<td>Multiple potential mechanisms (e.g., VEGF inhibition)</td>
<td>Gradual onset of renal failure occurs over weeks or months.</td>
<td>Removal of drug, supportive care</td>
</tr>
<tr>
<td>Complement-mediated TMA</td>
<td>Antibody inhibition of complement factor H activity</td>
<td>Initial presentation is acute kidney injury in children or adults.</td>
<td>Plasma exchange, immunosuppression, anti-complement agent</td>
</tr>
</tbody>
</table>
Hopkins TMA Registry

- TTP: 50%
- Other TMA: 33%
- aHUS: 13%
- STEC-HUS: 4%
Histopathology

Thrombotic Microangiopathies Result from Abnormalities in or Injury to Endothelial Cells

- TTP-TMA with platelet-rich thrombus
- HUS-TMA with subendothelial
- Preeclampsia with endotheliosis

Expansion
Pathophysiology of TMA

- **Chemotherapy, total body radiation**
- **Ischemia-reperfusion injury, rejection, CNI and m-TOR inhibitors**
- **High estrogen levels e.g. pregnancy**
- **Infections: EHEC, aspergillus, CMV, EBV, H1N1, pneumococci**

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**Endothelial dysfunction**

- **C3a, C5a, TCC**

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**Endothelial injury**

- **Complement dysregulation**
- **Large Artery Stenosis**
- **Endothelial detachment, leukocyte migration, Reactive cell proliferation, thrombosis, spasms, ischemia**

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**TMA**

- **Vasculopathy of Microvessels**
- **Gangrene of fingers and toes, skin ulcer, heart injury, CNS infarction and dysfunction, multiorgan failure**

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Hofer. Front Pediatric 2014
Complement Pathway

Lectin pathway

Classical pathway

Alternative pathway

C3 convertase (C4b2a)

C3

C3a

C3b

C5

C5 convertase (C4b2aC3b)

C5 convertase (C3bBbC3b)

C5b

Terminal complement cascade

C6 C7 C8 C9

C5b-9 (MAC)

CFH
CFI
MCP
Factor H-related proteins

Uncontrolled Complement Activation

Diagram showing the consequences of chronic uncontrolled complement activation, with pathways involving the lectin, classical, and alternative pathways. The diagram includes consequences such as immune complex clearance, microbial opsonization, and terminal complement activation leading to anaphylaxis, inflammation, and thrombosis.
What is Atypical HUS (aHUS)?

**LABORATORY FINDINGS**

- **Microangiopathic hemolytic anemia**
  - ↓ Hemoglobin
  - ↓ Haptoglobin
  - ↑ LDH
  - Schistocytes

- **Thrombocytopenia**
  - <150,000 per μL or
  - >25% ↓ baseline

- **Complement C3**
  - ↓ or ↑

- **Others**
  - ADAMTS13 activity: >5–10%
  - STEC culture/PCR: negative

**CLINICAL MANIFESTATIONS**

- **Kidney**
  - ↓ GFR
  - Proteinuria
  - Hematuria
  - Hypertension

- **CNS**
  - Altered mental status
  - Focal neurological deficits
  - Seizure

- **GI tract**
  - Diarrhea
  - Nausea/vomiting
  - Abdominal pain

Asif. Open Uro & Neph J 2015
Complement Amplifying Conditions precipitate aHUS

69% of patients had their first clinical manifestation while experiencing a complement-amplifying condition (N=191)[a]

Less Frequent Conditions
- Malignant hypertension 8%
- Transplant-associated 5%
- Glomerulopathy 4%
- Systemic disease* 2%
- Malignancy 1%

More Frequent Conditions
- Diarrhea/gastroenteritis 24%
- Upper respiratory tract infection 18%
- Pregnancy-associated 7%

20% aHUS unmasked by one of these complement-amplifying conditions

49% aHUS unmasked by one of these complement-amplifying conditions

31% aHUS with no report of a known complement-amplifying condition
Genetic Pathways to aHUS

Classical pathway
- C1
- C2
- C4
- C4b2a
- C3bBb
- C3

Alternative pathway
- CD46/MCP
- Factor I
- Factor H
- C3b
- C3

Activated factor VII
- Tissue factor
- Membrane attack complex
- C5a
- C3b
- Fibrin

Anti-factor H antibodies

Coppo, Drug Targets 2009
## Frequency of Mutations in aHUS

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency (%)</th>
<th>Recurrence (%)</th>
<th>Graft Loss (% recurrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH Mutations</td>
<td>20-30</td>
<td>76</td>
<td>86</td>
</tr>
<tr>
<td>CFH Autoantibody</td>
<td>6</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>CFI Mutations</td>
<td>4-10</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>MCP Mutations</td>
<td>10-15</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>C3 Mutations</td>
<td>5-10</td>
<td>50</td>
<td>80</td>
</tr>
</tbody>
</table>

~ 50% will have no mutations

Noris, NEJM 2009
The Problem with aHUS

Complement Mediated TMA

- Breast, Ovarian
- Gastric, colon
- Lung
- Pancreatic
- Lymphoma
- Systemic lupus erythematosus
- Antiphospholipid Syndrome
- Scleroderma
- Dermatomyositis
- Bone marrow transplant
- Solid Organ Transplant
- Influenza H1/N1
- Hepatitis A or C
- HIV
- Coxsackie B virus
- Epstein-Barr Virus
- Dengue
- HHV6
- Human Parvovirus B19
- Bordetella pertussis
- Cytomegalovirus
- Varicella
- Haemophilus influenzae
- Cytomagalovirus
- Clostridium difficile
- Norovirus
- Campylobacter
- streptococcal
- pneumoniae
- Ceftriaxone
- Ibuprofen
- Quinine
- Clopidogrel
- Alentuzumab
- Giprofoxacin
- Heroin, ecstasy
- Cocaine
- Contraceptives
Diagnosis of Exclusion

**Thrombocytopenia**
- Platelet count <150,000/µL or >25% decrease from baseline

**Microangiopathic hemolysis**
- Schistocytes and/or elevated LDH, decreased haptoglobin, and/or decreased hemoglobin

**Target organ damage**
- Neurologic, renal, gastrointestinal, cardiovascular, etc.

Evaluate ADAMTS13 activity and Shiga-toxin/EHEC

While awaiting ADAMTS13 results: if platelet count >30,000/µL or serum creatinine >1.7-2.3 mg/dL, can almost eliminate possibility of severe ADAMTS13 deficiency (TTP)[a]

- ≤5% ADAMTS13 activity[b]
  - TTP

- >5% ADAMTS13 activity[b]
  - aHUS

- Shiga-toxin/EHEC positive[b]
  - STEC-HUS
Complement Activation might be a Common Pathway to all TMAs

Complements in Kidney Disease

MBL Activation

- IgA nephropathy
- Membranous nephropathy
- Post-streptococcal glomerulonephritis

Immune-complex deposition

- Lupus nephritis
- Membranous disease
- MPGN I and III
- IgA nephropathy

Dysregulated Activation of the Alternative Pathway

- Atypical HUS
- C3 glomerulopathy
- Dense Deposit Disease
- Ischemic acute kidney injury
- ANCA associated vasculitis
- Post-streptococcal glomerulonephritis

Antibody to renal antigens

- Antibody mediated rejection of renal allografts
- Anti-GBM disease

Thurman. AJKD 2015
Thrombotic Thrombocytopenic Purpura (TTP)
TTP

- Fever
- Thrombocytopenia, Hemolytic Anemia
- Neurologic symptoms (seizures/strokes), Renal Failure
- ADAMTS13<5%

Acquired TTP (>95% cases)
- ADAMTS13 AutoAntibody Present (IgG inhibitor)
- High Risk of Recurrence If No Therapy

Hereditary TTP (Upshaw Schulman Syndrome)
- No Autoantibody Present
- Mutations in ADAMTS13 Gene resulting in inadequate gene expression
- Kidney Transplant Contra-Indicated

Shenkman, Autoimmun Reviews 2014
TMA and Kidney Transplantation

• **De Novo**
  - Drugs: CNI (CYA, Tacrolimus), mTOR inhibitors
  - Acute AMR
  - Infections

• **Recurrent**
  - Variable risk with TTP
  - aHUS: up to 60% recurrence with up to 90% graft failure
  - Can recur within a few days to 2 years (60% in 1\textsuperscript{st} month)
TMA Diagnostic Algorithm

- Evidence of MAHA/TMA
  - CBC, Smear
  - LDH, Haptoglobin
  - PT, PTT, INR
- Infections
  - STEC (if diarrhea)
  - Influenza
  - HIV, CMV
- Autoimmune Disease
  - SLE testing
  - Antiphospholipid Antibodies
- Complement Abnormalities
- Drugs
  - Ticlopidine, Gemcitabine, Quinine
  - Tacrolimus/Cyclosporin
- Transplant: AbMR
Where to send the complement testing?

- University of Iowa (MORL) – turnaround 2-4 weeks
- Blood Center of Wisconsin – turnaround 2-4 weeks
- University of Cincinnati – turnaround 2-4 weeks
- Machaon Diagnostics – turnaround 4-5 days
  - No functional testing available
## What to send?

<table>
<thead>
<tr>
<th>Kidney Testing</th>
<th>CPT Codes</th>
<th>Cost</th>
<th>TAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetic Renal Panel</strong> (previously known as the TMA Panel) (CFH, CFI, MCP, CFB, CFHR5, C3, THBD, ADAMTS13, PLG, DGKE, and MLPA)</td>
<td>81479(x11)</td>
<td>$3,000</td>
<td>28 days</td>
</tr>
<tr>
<td>MLPA (screen for deletions of CFHR1-CFHR3)</td>
<td>81479</td>
<td>$624</td>
<td>8-12 weeks</td>
</tr>
<tr>
<td>Familial Mutation Testing</td>
<td>81403</td>
<td>$200</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>TMA Functional Panel</strong> (FH autoantibody, Hemolytic Assay, CH50, APFA, FH, FI, FB, C3, C4, ADAMTS-13 &amp;sC5b-9)</td>
<td>85397, 86160(x5), 86161(x2), 86162</td>
<td>$2,272</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>C3G Functional Panel</strong> (FB autoantibody, FH autoantibody, Hemolytic Assay, C3NeF, C4Nef, CH50, APFA, C3, C3d, FB, Ba, Bb, C5, Properdin, &amp; sC5b-9)</td>
<td>86160(x7), 86161(x5), 86162, 86334</td>
<td>$4,063</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

This data should NOT be used to guide therapy. 50% of patients with aHUS have no mutations.

[http://www.medicine.uiowa.edu/morl/testingmenu/](http://www.medicine.uiowa.edu/morl/testingmenu/)
Management of TMAs

- Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Immune</td>
</tr>
<tr>
<td><strong>Leg cramps, other minor symptoms, malaria</strong></td>
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<tr>
<td>Quinine</td>
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<tr>
<td><strong>Cancer therapy</strong></td>
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<tr>
<td>Bevacizumab</td>
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<tr>
<td>Gemcitabine</td>
<td>X</td>
</tr>
<tr>
<td>Mitomycin</td>
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<tr>
<td>Oxaliplatin</td>
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<tr>
<td>Pentostatin</td>
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<tr>
<td>Sunitinib</td>
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<tr>
<td><strong>Antibiotic</strong></td>
<td></td>
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<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td></td>
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<tr>
<td><strong>Immunosuppressive therapy</strong></td>
<td></td>
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<tr>
<td>Cyclosporine</td>
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<tr>
<td>Interferon</td>
<td></td>
</tr>
<tr>
<td>Sirolimus</td>
<td>X</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
</tr>
<tr>
<td><strong>Drugs of abuse</strong></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>X</td>
</tr>
<tr>
<td>Ecstasy (MDMA, also known as Molly)</td>
<td>X</td>
</tr>
<tr>
<td>Oxycodeine extended release (Opana ER)</td>
<td>X</td>
</tr>
</tbody>
</table>
CNI Induced TMA

- Unclear incidence.
- Drug Conversion is usually the favored option.
- It is possible that several of these cases had aHUS.
# Plasma Exchange/Infusion

<table>
<thead>
<tr>
<th><strong>TTP</strong>(^a)</th>
<th><strong>aHUS</strong>(^g,h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient ADAMTS13 activity (≤5%) leaves von Willebrand factor intact(^b-d)</td>
<td>Genetic defects lead to chronic uncontrolled activation of the complement system</td>
</tr>
<tr>
<td>Treatment goal: suppress inhibitor autoantibody; replace ADAMTS13</td>
<td>Treatment goal: inhibit ongoing complement activation</td>
</tr>
<tr>
<td>PE/PI replenishes ADAMTS13 and decreases autoantibodies(^e,f)</td>
<td>PE/PI fails to inhibit complement activity that drives pathophysiology in aHUS</td>
</tr>
</tbody>
</table>
Plasma Exchange/Infusion Does Not Improve Graft Survival in aHUS Recurrence

Le Quintrec, AJT 2013
Eculizumab

• First-in-class humanized antibody against complement C5
• Marketed as “Soliris” by Alexion Pharmaceuticals
• Prevents formation of C5b-C9 “membrane attack complex” MAC
• Approved for use in PNH and aHUS
Eculizumab for Atypical Hemolytic Uremic Syndrome Recurrence in Renal Transplantation

Zuber AJT 2012
The complement cascade with the target values for therapeutic drugs

Frémeaux-Bacchi, Kidney International 2015
Eculizumab for refractory TTP
Eculizumab for congenital TTP

Pecoraro, AJKD 2015
Case 1

- 38yoWM with a h/o 2 failed kidney transplants. Diagnosed with aHUS at the age of 15 months.
  - Received 3rd DDRT at VCUHS in April 2014.
  - On maintenance eculizumab q2weekly.
  - Serum creatinine=1.8mg/dL.
### Case 2

#### Day 0
- 48yoWF with a h/o strokes
- LURT Feb 2015

#### Day 1
- TMA on Post-op Day 1
- Labs to evaluate for aHUS and TTP sent.
- Received eculizumab, RBCs and platelets with recovery

#### Day 14
- Relapse
- ADAMTS13<5%
- No Auto-antibody.

#### Day 17
- Diagnosed with hereditary TTP (Upshaw Shulman Syndrome)
- Started on Plasma Infusions for ADAMTS13 repletion

#### Day 60
- Genetic testing with 2 mutations in ADAMTS13 Gene
- Sister who has a history of strokes and eclampsia has the same mutations.
Case 2 – Clinical Course

Maintenance Tacrolimus, Mycophenolate, Prednisone

Chart showing trends in serum creatinine and hemoglobin over time post-transplant.
Case 3

- 21yo brain dead donor
  - Died of gunshot wound to the head.
  - Terminal Creatinine 3.2mg/dL
  - Hb 11.7; INR 1.5; Plt 24
  - Biopsies with extensive glomerular fibrin micro-thrombi
  - Initial pump numbers poor. Declined by Kentucky OPO.
  - Brought to VCUHS and re-pumped.
    - Right Kidney=Res: 0.3; Flow=103
    - Left Kidney=Res=0.2; Flow=119
  - Transplanted in two local patients with no h/o TMA
Case 3a - Clinical Course

**Hemoglobin**

- g/dL

**PLT**

- 10e9/L

**INR**

- 1.5

Case 3a- Clinical Course

Pre-implantation Bx

Week 3 Bx
Case 3b – Clinical Course

Hemoglobin

PLT

INR
Case 3 – Not all hemolysis is related to recipient disease

- Donor-derived DIC

Deranged coags
INR, PTT, Fibrinogen, D-dimer

Kurosawa, J Intensive Care 2014
Case 3

• Donor DIC has usually been reported in the setting of gunshot wounds to the head.
• Seems to self-resolve with time.
Case 4

- 22yo brain dead donor
  - Died of gunshot wound to the head.
  - Terminal Creatinine 3.2mg/dL
  - Hb 8.8; INR 1.7; Plt 58
  - No biopsies performed.
  - Donor blood cultures were positive for Clostridium septicum.
  - Transplanted in two local patients with no h/o TMA
    - 3yo male
    - 72yo female
Case 4a - Not all hemolysis is TMA
Case 4b - Not all hemolysis is TMA
C. Septicum Alpha Toxin is Hemolytic

**FIG. 1.** Growth of *C. septicum* and expression of alpha-toxin. Shown is the growth of *C. septicum* BX96 and the expression of hemolytic activity. More than 95% of the hemolytic activity was attributed to alpha-toxin, and therefore the observed activity reflects primarily alpha-toxin expression during the growth.
Case 4

- Our kidney transplant patients were started on PCN based prophylaxis x 6 months.

- Prophylaxis for the UVA OLT Patient was stopped at approximately 3 months post-transplant.

- A few weeks later he presented with fevers and empyema. Cultures grew C. septicum.

- Current Status
  - C. septicum sent to Idaho to assess for hemolytic activity.
Questions

• Special thanks to –
• Alex Clay
• Dr Dhiren Kumar
• Dr Anne King
• Transplant Nurse Co-ordinators
• Oklahoma – Dr James George
• Oklahoma – Dr Rodney Tweten
• Wisconsin – Dr Kenneth Friedman
• Idaho – Dr Dennis Stevens
• UVA – Dr Sifri Costi
### Activation Pathways of Complement

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Initiators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Immune complexes, apoptotic cells, certain viruses and gram-negative bacteria, C-reactive protein bound to ligand</td>
</tr>
<tr>
<td>Mannose-binding lectin</td>
<td>Microbes with terminal mannose groups</td>
</tr>
<tr>
<td>Alternative</td>
<td>Many bacteria, fungi, viruses, tumor cells</td>
</tr>
</tbody>
</table>
Sites of complement pathway dysregulation.

A. Loss of CFH Inhibition

B. CFH Deregulation

C. Stabilization of the C3 Convertase

D. Impaired Inactivation of C3b to iC3b

An S. De Vriese et al. JASN doi:10.1681/ASN.2015020184
Sites of Complement-mediated Renal Injury

Fearn, World J Nephrol 2015
Managing and preventing atypical hemolytic uremic syndrome recurrence after kidney transplantation. Noris, Marina; Remuzzi, Giuseppe

Current Opinion in Nephrology & Hypertension. 22(6):704-712, November 2013. DOI: 10.1097/MNH.0b013e328365b3fe

FIGURE 2. Schematic representation of graft outcome in the seven published atypical hemolytic uremic syndrome (aHUS) patients who experienced a relapse following initiation of eculizumab treatment. All patients were receiving eculizumab for treatment of a preceding aHUS recurrence in the graft. Time zero in the scale corresponds to the start of eculizumab administration. Patients number 1 and 2 received a single eculizumab dose. Patients number 3 and 6 had delays of 6 and 8 days (#3) and 7 days (#6) between two subsequent doses of eculizumab. In patients number 4 and 5, eculizumab was interrupted for 3 and 5 months, respectively, and then resumed following disease recurrence. Ecu, eculizumab.
Representative kidney biopsy findings in aHUS.
Representative kidney biopsy findings from a single patient with (A–C) DDD and (D–F) C3 GN.  
(A) Light microscopy shows a membranoproliferative pattern of injury with thickened GBMs and mesangial and endocapillary proliferation.

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Table 2. Complement Testing in Patients With C3 Glomerulopathy

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 and C4 levels</td>
<td>C3 frequently depressed and supports diagnosis; normal C4 suggests an alternative pathway process</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Soluble C5b-9</td>
<td>May be indicator of active disease; may identify patients who will benefit from C5 blockade</td>
<td>Test not widely available</td>
</tr>
<tr>
<td>C3 nephritic factor</td>
<td>Associated with C3 glomerulopathy; may identify patients who will benefit from B-cell–targeted therapies</td>
<td>Levels do not correlate with disease activity; also seen in MPGN type 1</td>
</tr>
<tr>
<td>Factor H protein levels</td>
<td>May identify underlying mechanism of alternative pathway activity; may identify patients who will benefit from plasma infusion/exchange</td>
<td>Test not widely available</td>
</tr>
<tr>
<td>Autoantibodies to factor H and factor B</td>
<td>May identify underlying mechanism of alternative pathway activity; may identify patients who will benefit from B-cell–targeted therapies</td>
<td>Test not widely available</td>
</tr>
<tr>
<td>Genetic mutation screening: Factor H; CFHR1, 2, &amp; 5; factor I; C3; factor B</td>
<td>May identify underlying mechanism of alternative pathway activity</td>
<td>Not widely available; clinical implications unknown</td>
</tr>
</tbody>
</table>

Abbreviations: CFHR, complement factor H–related protein; MPGN, membranoproliferative glomerulonephritis.
Table 3. Complement Testing in Patients With aHUS

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 and C4</td>
<td>Low C3 supports that disease involves the complement system; normal C4 suggests an alternative pathway process</td>
<td>An insensitive indicator of complement activation in aHUS</td>
</tr>
<tr>
<td>Soluble C5b-9</td>
<td>A sensitive indicator of complement activation and also may reflect active disease</td>
<td>Test not widely available</td>
</tr>
<tr>
<td>Levels of factor H, factor I, MCP</td>
<td>May identify underlying mechanism of alternative pathway activity</td>
<td>Levels may be normal in patients with dysfunction protein</td>
</tr>
<tr>
<td>Autoantibodies to factor H</td>
<td>May identify underlying mechanism of alternative pathway activity</td>
<td>Test not widely available</td>
</tr>
<tr>
<td>Genetic mutation screening:</td>
<td>May identify underlying mechanism of alternative pathway activity</td>
<td>Tests not widely available; tests take too long to help with acute care</td>
</tr>
<tr>
<td>Factor H; MCP; factor I; C3; factor B; thrombomodulin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aHUS, atypical hemolytic uremic syndrome; MCP, membrane cofactor protein.
MPGN I

Usually C3
Variable Ig

DDD

Always C3
Little/No Ig
Pathophysiology of TMA