Clinical Challenges in Hematology -- Anemia

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Conflicts of Interest

• UpToDate
  – Section Editor & Author
  – Royalties

• I do not have other financial relationships with proprietary entities producing health care goods or services
Clinical Questions to be Addressed

- What are “don’t miss” causes of iron deficiency?
- What are “don’t miss” causes of hemolysis?
- What are diagnostic challenges in vitamin B12 deficiency?
- Who should be referred for bone marrow biopsy?
Case # 1

• A 55-year male chemist develops fatigue
• 5 years ago at age 50, he had normal screening colonoscopy with visualization of the ileocecal valve and appendiceal orifice
• With a family history of heart disease, he takes aspirin 81 mg daily and drinks a glass of wine with dinner nightly
• Family history: no known malignancies or hematologic abnormalities
Case # 1 continued

- Physical exam is entirely normal
- CBC
  - RBC = 3.80 million/μL (normal, 4.5-6.2)
  - Hgb = 10.5 g/dL (normal, 14.0-18.0)
  - HCT = 30.8% (normal, 40-52)
  - MCV = 79 fL (normal, 82-98)
  - MCH = 24 pg/RBC (normal, 27-32)
  - MCHC = 34 (31-35)
- WBC with differential and platelet count are normal
- Peripheral blood smear (see next slide)
Hypochromic, microcytic RBCs, cigars and pencils in IDA
Case # 1 continued

- Serum iron chemistries
  - Iron = 9 μ/dL (normal, 45-160)
  - Calculated TIBC = 460 μ/dL (normal, 260-470)
  - Ferritin = 15 ng/mL (normal, 30-400)
- Fecal cards obtained at home are heme-positive
- Colonoscopy is normal to cecum with visualization of appendiceal orifice
- EGD
  - Gastritis; biopsy negative for *H. pylori*
  - Duodenum appears normal; biopsy not obtained
Case # 1 continued

• He stops aspirin and begins proton pump inhibitor + non-timed-release formulation ferrous gluconate (27 mg of elemental iron) + ascorbic acid 250 mg
  – Once daily 45 minutes after his evening meal
  – 2 weeks later, he increases his iron regimen to twice daily, once after lunch and once after his evening meal
Case # 1 continued

• 6 weeks later, he returns for re-evaluation
  – He notes persistent fatigue
  – Stools are black but negative for occult blood
  – CBC remains unchanged
  – Ferritin level remains low at 15 ng/mL

• His primary care physician refers him to a hematologist
Case # 1 continued

• He denies drinking tea or taking calcium supplements with his iron supplement

• Additional labs:
  • tTG-IgA = 112 units
Case # 1:
Duodenal biopsy shows celiac sprue

- Celiac sprue should be considered in any patient with IDA and documented impaired iron absorption, even without GI symptoms
  - In 1 study of pts with unexplained IDA, 11 of 93 (12%) were found to have celiac sprue on small bowel biopsy¹

- Tissue transglutamic acid-immunoglobulin A
  - Generally increased with active celiac sprue
  - False normal levels in pts with IgA deficiency, which is more common in pts with celiac sprue

- At EGD, gross macroscopic duodenal findings of celiac sprue can be quite subtle
  - Duodenal biopsies should be obtained routinely at EGD in pts with unexplained IDA, with or without documented impaired iron absorption²

Case # 2

- 55-year old Russian male on disability following work-related injury in metal industry
- In 2002, underwent Roux-en-Y gastric bypass surgery for obesity management. He takes supplements of iron & vitB12
- In 2010, referred to hematology for iron deficiency anemia with ferritin = 4.7 ng/mL
  - Iron/TIBC = 47/490; vitB12 = 659 pg/mL
  - HGB = 10.9; HCT = 36.7; MCV = 77; MCH = 23.0; MCHC = 29.8; RDW = 18.4
- Colonoscopy normal to cecum
- EGD
  - Congestion and erythema in whole stomach pouch compatible with gastritis
  - Efferent jejunal limb and blind jejunal end
  - Steiner stain of gastric biopsy negative for *H. pylori*
Case # 2 has an oral iron challenge test

Following an overnight fast, blood is drawn at time 0, and he swallows 1 mL of ferrous sulfate solution (15 mg of elemental iron) admixed with a glass of orange juice. Blood samples are drawn hourly thereafter.

<table>
<thead>
<tr>
<th>Time (in minutes)</th>
<th>Serum iron level (μ/dL)</th>
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<tbody>
<tr>
<td></td>
<td>Patient</td>
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<tr>
<td>0</td>
<td>86</td>
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<tr>
<td>30</td>
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</tr>
<tr>
<td>60</td>
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</tr>
<tr>
<td>90</td>
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<td>120</td>
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<td>150</td>
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<tr>
<td>180</td>
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Case # 2 receives parenteral iron

<table>
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<tr>
<th>Date</th>
<th>Ferumoxytol</th>
<th>Ferritin</th>
<th>HGB</th>
<th>HCT</th>
<th>MCV</th>
<th>MCH</th>
<th>MCHC</th>
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<tr>
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<td>4.7</td>
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<td>03/17/10</td>
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<tr>
<td>03/24/10</td>
<td>510 mg</td>
<td>---</td>
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<td>28</td>
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<tr>
<td>08/26/10</td>
<td>510 mg</td>
<td>---</td>
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</tr>
<tr>
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<td>14.7</td>
<td>42.9</td>
<td>92</td>
<td>31.5</td>
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<td>09/13/11</td>
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<td>64</td>
<td>15.2</td>
<td>43.6</td>
<td>92</td>
<td>32.3</td>
<td>34.9</td>
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Iron Salts versus Polysaccharide-iron Complexes

• Iron salt formulations (NOT “time-release”)
  – Release iron in the duodenum
  – Iron is best absorbed from the duodenum and proximal jejunum

• Polysaccharide-iron complexes, enteric coated or sustained release capsules (e.g., Niferex® 150)
  – Release iron further down GI tract where iron is not absorbed
  – Counterproductive
  – More expensive than simple iron salt tablets
Factors Influencing Dietary Iron Absorption

• Positive factors
  – Ascorbic acid
  – Meat or fish

• Negative factors
  – Phytate (in bran, oats, rye fiber)
  – Polyphenols (in tea, some vegetables and cereals)
  – Dietary calcium
  – Soy protein
  – Inhibition of gastric acid secretion
Optimizing Patient Acceptance in Oral Iron Therapy

- Administer small doses with or after meals
- Increase dose amounts as tolerated
  - Once daily for 2 weeks
  - Twice daily thereafter, if tolerated
  - Very few patients tolerate thrice daily iron
- Administer stool softeners proactively
Blood Loss Is the Most Common Cause of Anemia

- **Obvious bleeding**
  - Trauma, melena, hematemesis, menometrorrhagia

- **Bleeding that is not always obvious**
  - Surgical bleeding, bleeding into the upper thigh or retroperitoneum, factitious bleeding

- **Iatrogenic bleeding**
  - Repeated phlebotomy, hemodialysis, blood donation

- **Occult bleeding**
AGA Definition of Occult Blood Loss

The initial presentation of a positive fecal occult blood test result and/or iron deficiency anemia, when there is no evidence of visible blood loss to the patient or physician

Zuckerman GR et al. Gastroenterology 2000;118:201
When Bleeding Is Not Evident

- Decreased iron absorption
  - Malabsorption
  - Diet
- Intravascular hemolysis
  - Paroxysmal nocturnal hemoglobinuria
  - Malfunctioning heart valves
- Pulmonary hemosiderosis
  - Anti-glomerular basement membrane antibody disease
- Erythropoietin administration
Considerations when patients do not respond to oral iron supplements

• Poor patient adherence
  – Oral iron exacerbates symptoms of underlying disease (e.g., inflammatory bowel disease)

• Continued bleeding

• Inability to absorb iron preparation
  – Gastric by-pass for obesity

• Coexisting condition
  – Inflammation (blocking iron utilization)
  – Renal failure (erythropoietin deficiency)

• Incorrect diagnosis
How I treat unexplained refractory iron deficiency anemia

Chaim Hershko¹ and Clara Camaschella²

¹Division of Quality Assurance, Israel Ministry of Health, Jerusalem, Israel; and ²Vite-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy

Endoscopic gastrointestinal workup fails to establish the cause of iron deficiency anemia (IDA) in a substantial proportion of patients. In patients referred for hematologic evaluation with unexplained or refractory IDA, screening for celiac disease, autoimmune gastritis, Helicobacter pylori, and hereditary forms of IDA is recommended. About 4% to 6% of patients with obscure refractory IDA have celiac disease, and autoimmune gastritis is encountered in 20% to 27% of patients. Stratification by age cohorts in autoimmune gastritis implies a disease presenting as IDA many years before the establishment of clinical cobalamin deficiency. Over 50% of patients with unexplained refractory IDA have active H pylori infection and, after excluding all other causes of IDA, 64% to 75% of such patients are permanently cured by H pylori eradication. In young patients with a history suggestive of hereditary iron deficiency with serum ferritin higher than expected for IDA, mutations involving iron trafficking and regulation should be considered. Recognition of the respective roles of H pylori, autoimmune gastritis, celiac disease, and genetic defects in the pathogenesis of iron deficiency should have a strong impact on the current diagnostic workup and management of unexplained, or refractory, IDA. (Blood. 2014;123(3):326-333)
Diagnostic workup preceding the recognition of unexplained refractory IDA

(Hershko C, Camaschella C. Blood 2014; 123:326-333)

Initial workup:
- Hb, MCV, Tf saturation, ferritin, TfR, ZPP, CHr

Category:
- Increased physiologic needs
- Low risk patients
- Males, Post-menopausal females

Detailed medical history, Occult blood
- negative: proceed to treatment
- positive: Unexplained Refractory IDA
  - no response

complete GI workup
  - no finding
  - no response
Proposed diagnostic workup for unexplained or refractory IDA  
(Hershko C, Camaschella C. Blood 2014; 123:326-333)

<table>
<thead>
<tr>
<th></th>
<th>$H\ pfy\lori$</th>
<th>Autoimmune gastritis</th>
<th>Celiac disease</th>
<th>IRIDA</th>
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<tbody>
<tr>
<td><strong>Screening</strong></td>
<td>$H\ pfy\lori$ IgG antibodies or fecal antigen</td>
<td>Serum gastrin anti-parietal Abs, anti-intrinsic factor Abs</td>
<td>tTG-IgA Abs</td>
<td>Suggestive history and clinical assessment</td>
</tr>
<tr>
<td><strong>Advanced</strong></td>
<td>Urease breath test; gastroscopy and biopsies (optional)</td>
<td>Gastroscopy and biopsies (recommended)</td>
<td>Duodenal biopsy, HLA screening for DQ2 or DQ8 genotypes</td>
<td>Sequencing of the TMPRSS6 gene</td>
</tr>
<tr>
<td><strong>Response to specific treatment</strong></td>
<td>$H\ pfy\lori$ eradication</td>
<td>NA</td>
<td>Gluten-free diet</td>
<td>NA</td>
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</table>

NA, not applicable; IRIDA, iron refractory iron deficiency anemia
Clinical Questions to be Addressed

• What are “don’t miss” causes of iron deficiency?
• What are “don’t miss” causes of hemolysis?
• What are diagnostic challenges in vitamin B12 deficiency?
• Who should be referred for bone marrow biopsy?
Hemolysis: General Approach

- **Congenital vs. acquired**
  - Membrane disorders; hemoglobinopathies; enzymopathies

- **Spherocytic vs. non-spherocytic**
  - Spherocytes (membrane; immune; phospholipase)
  - Bite cells (oxidant stress; methemoglobin)
  - Schistocytes (fragmentation)
  - Spur cells (liver disease)
  - Malaria; babesiosi

- **Immune vs. non-immune**
  - Coombs testing (IgG, C3)

- **Intramedullary vs. extramedullary**
  - Intravascular (urine hemosiderin, hemoglobinuria)
  - Extravascular (spleen, RES)
Examination of the blood smear is key.
Microcytic, hypochromic RBCs, targets and sickle forms in S-β^+ thalassemia
Spherocytes in warm autoimmune hemolytic anemia
Macrophage Ingesting an IgG-Coated RBC

RBC aggregates in cold agglutininin disease
IgG and IgM Binding RBC Antigens
Numerous spherocytes from phospholipase digestion of RBCs in clostridial sepsis
Erythrophagocytosis in EBV infection
Spur cell hemolytic anemia in liver disease
Case # 3

24-yo woman develops headaches and fevers. On exam, she appears restless with dysarthric speech. T = 100.5°F.

- HCT = 28%; HGB = 9.7 g/dL; MCV = 102 fL
- WBC = 6.6 K/µL with 55% polys, 3% bands, 30% lymphs, 8% monos, 4% NRBCs
- Platelets = 5 K/µL; PT = 12.1 sec; aPTT = 24.3 sec
- Retic count = 6.6%; LDH = 546 IU/L; total bili = 1.1 mg/dL; haptoglobin < 20 mg/dL
- Creatinine = 0.5 mg/dL
Schistocytes, NRBC, decreased platelets
Thrombotic Microangiopathies (alias Microangiopathic Hemolytic Anemias)

- Disseminated intravascular coagulation
  - Infections
  - Obstetrical disorders
  - Other causes
- Malignant hypertension
- Disseminated carcinoma
- Giant hemangioma
- TTP
  - Pregnancy
  - Autoimmune disorders
  - HIV
  - E. coli O157:H7, O104:H4
- HUS
- Immunologic vasculitis
- Antiphospholipid antibody syndrome
- Mitomycin, ticlopidine, quinine, cyclosporine
TTP: Lab Manifestations

- Red cell fragmentation can be extreme
  - Even to the extent of decreasing red cell mean corpuscular volume (MCV) and artifactually increasing reported platelet counts

- Serum lactate dehydrogenase (LDH) level is typically extremely high
  - Reflecting hemolysis and tissue damage due to systemic ischemia
Pathogenesis of Idiopathic TTP Caused by ADAMTS13 Deficiency
Sadler JE. Blood 2008; 112:11-18
ADAMTS13 Activity Predicts Relapse Risk

Kaplan-Meier curve of time to first relapse. The y-axis shows the relapse-free survival distribution function, whereas x-axis indicates years of follow-up. Forty-seven surviving patients with ADAMTS13 activity < 10% and 136 patients with ADAMTS13 ≥ 10% were analyzed.
ADAMTS13 Assays

• Assay results for the von Willebrand factor cleaving protease (ADAMTS13) and its inhibitor are not readily available

• Other reasons for decreased ADAMTS13 activity
  – HIT, severe sepsis, liver cirrhosis, chronic uremia, ITP, DIC, SLE, leukemia, pregnancy, post-op, neonatal age, advanced age
Biv  Thrombin proteolytically inactivates ADAMTS13, preventing destabilization of the platelet plug.
Thrombocytopenia and MAHA without another clinically apparent cause (e.g., DIC, malignant hypertension): Warrants suspicion of TTP-HUS and initiation of steroids + plasma exchange

Alternative diagnosis: Stop plasma exchange

ADAMTS13 activity normal: Stop steroids; debate role of plasma exchange

ADAMTS13 inhibitor present: Continue steroids

ADAMTS13 inhibitor present with refractory-relapsing TTP: Consider rituximab

**DIAGNOSIS**
- Begin daily PEX, with plasma replacement

**ADAMTS13 deficiency not suspected (e.g., acute renal failure present, drug-induced or Shiga toxin etiology suspected)**
  - No steroids
  - Continue PEX until response

**ADAMTS13 deficiency suspected**
- Begin steroids

**RESPONSE**
Platelet count >150,000/µL for 2 days
- Stop PEX
- Continue steroids
- Maintain CVC

- Platelet count remains normal for 1-2 weeks
  - Remove CVC
  - Taper steroids

**REMISSION**
Platelet count remains normal for 30 days after last PEX

**EXACERBATION**
(recurrent thrombocytopenia)
- Resume daily PEX
- Rituximab

**RELAPSE**
- Daily PEX
- Steroids
- Rituximab

**Alternative etiology discovered**
- Stop PEX

**No or transient response, new neurologic abnormality**
Consider:
- High-dose steroids
- Rituximab
- Twice-daily PEX

**Platelet count increase, neurologic improvement**
- Resume daily PEX
A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura

Marie Scully,1 Vickie McDonald,2 Jamie Cavenagh,3 Beverley J. Hunt,4 Ian Longair,1 Hannah Cohen,1 and Samuel J. Machin4

1Department of Haematology, University College London Hospital, London, United Kingdom; 2Haemostasis Research Unit, University College London, London, United Kingdom; 3Department of Haematology, St Bartholomew’s and the London Hospital, London, United Kingdom; and 4Department of Haematology, Guys and St Thomas’ National Health Service Foundation Trust, London, United Kingdom

The safety and efficacy of weekly rituximab 375 mg/m² (×4), given within 3 days of acute TTP admission, with standard therapy (PEX and steroids) was evaluated. Clinical outcomes were compared to historical controls (n = 40) who had not received rituximab. Within the trial group, 15 of 40 required ICU admission and 15% of all cases with the highest troponin T levels on admission were ventilated. Before the second rituximab infusion, 68% of cases had a platelet count > 50 × 10⁹/L and 38% > 150 × 10⁹/L. Fewer PEX were required in whites compared to nonwhite in the rituximab group (mean 14 vs 21, P = .0095). Inpatient stay was reduced by 7 days in the non-ICU trial cases compared to historical controls (P = .04), especially in whites, with a mean reduction of 7 days (P = .05). Ten percent of trial cases relapsed, median 27 months (17-31 months), compared to 57% in historical controls, median 18 months (3-60 months; P = .0011). There were no excess infections or serious adverse events with rituximab. In conclusion, rituximab appears a safe and effective therapy. Inpatient stay and relapse are significantly reduced in the rituximab cohort. Rituximab should be considered in conjunction with standard therapy on acute presentation of TTP. This study was registered at www.clinicaltrials.gov as NCT009-3713. (Blood. 2011;118(7): 1746-1753)
Final Comments

• Avoid platelet transfusion in patients with TTP except for management of life threatening hemorrhage

• To date, there is no defined role for monitoring ADAMTS13 activity after recovery
Recommended Reading

Syndromes of Thrombotic Microangiopathy

James N. George, M.D., and Carla M. Nester, M.D.

<table>
<thead>
<tr>
<th>Name</th>
<th>Cause</th>
<th>Clinical Features</th>
<th>Initial Management</th>
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<tr>
<td>Hereditary disorders</td>
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<tr>
<td>ADAMTS13 deficiency—</td>
<td>Homozygous or compound heterozygous ADAMTS13 mutations</td>
<td>Initial presentation is typically in children but may also be in adults; possible</td>
<td>Plasma infusion</td>
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<td>mediated TMA (also called</td>
<td></td>
<td>evidence of ischemic organ injury; acute kidney injury is uncommon; patients</td>
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</tr>
<tr>
<td>TTP)</td>
<td></td>
<td>with heterozygous mutations are asymptomatic.</td>
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<tr>
<td>Complement-mediated TMA</td>
<td>Mutations in CFH, CFI, CFB, C3, CD46, and other complement genes</td>
<td>Initial presentation is often in children but may also be in adults; acute kidney</td>
<td>Plasma infusion or exchange,</td>
</tr>
<tr>
<td></td>
<td>causing uncontrolled activation of the alternative pathway of</td>
<td>injury is common; patients with heterozygous mutations may be symptomatic.</td>
<td>anti-complement agent</td>
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<tr>
<td>Metabolism-mediated TMA</td>
<td>Homozygous mutations in MMACHC (encoding methylmalonic aciduria and</td>
<td>Initial presentation is typically in children &lt;1 year of age; also reported in</td>
<td>Vitamin B₁₂, betaine, folic</td>
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<tr>
<td></td>
<td>homocystinuria type C protein)</td>
<td>one young adult with hypertension and acute kidney injury.</td>
<td>acid</td>
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<td>Coagulation-mediated TMA</td>
<td>Homozygous mutations in DGKE; mutations in PLG and THBD also</td>
<td>Initial presentation with acute kidney injury is typically in children &lt;1 year of</td>
<td>Plasma infusion</td>
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<tr>
<td></td>
<td>implicated</td>
<td>age with DGKE mutations; clinical features of disorders associated with other</td>
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<tr>
<th>Name</th>
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<th>Initial Management</th>
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<tr>
<td>ADAMTS13 deficiency–mediated TMA</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>
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<tr>
<td>(also called TTP)</td>
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<tr>
<td>Shiga toxin–mediated TMA (also called ST-HUS)</td>
<td>Enteric infection with a Shiga toxin–secreting strain of <em>Escherichia coli</em> or <em>Shigella dysenteriae</em></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>
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<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>
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<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>
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<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, anticomplement agent</td>
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* The primary TMA syndromes are described by evidence supporting a defined cause. Shiga toxin–mediated TMA (also called Shiga toxin–related hemolytic–uremic syndrome [ST-HUS]) occurs primarily in children and may be the most common of the nine primary TMA syndromes. Among adults, acquired thrombotic thrombocytopenic purpura (TTP) may be the most common primary TMA syndrome; acquired TTP is rare in children, in whom the incidence may be similar to that of hereditary TTP. The frequencies of TMA that are mediated by complement, metabolism, coagulation, or drugs are unknown. The demonstration of antibodies that can neutralize the activity of complement factor H suggests that acquired TMA mediated by a deficiency in complement factor H may occur. DGKE denotes diacylglycerol kinase ε, PLG plasminogen, THBD thrombomodulin, and VEGF vascular endothelial growth factor.