



ANNALS OF B POD

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BLOOD

*ULNAR ARTERY 4
PSEUDOANEURYSM*

AND

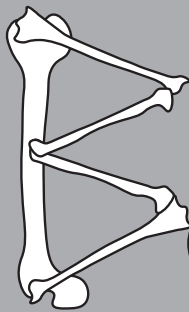
*2 DISSEMINATED
INTRAVASCULAR
COAGULATION*

*Cecal 10
Volvulus*

GUTS

AND

*12 Maisonneuve
Fracture*



Bones that Bust,



*That's What B-POD
is Made Of!*

2 **DIC** *Shaw*
 4 **Ulnar Artery Pseudoaneurysm**
Klaszky
 6 **TTP** *Baez*
 8 **Antiplatelet Reversal in Intracerebral Hemorrhage** *Nardone*
 10 **Cecal Volvulus** *Ham*
 12 **Maisonneuve Fracture** *Banning*
 Back **EKG Focus: Cerebral T Waves**
 Cover *Lagasse*

The Winter issue of Annals of B Pod highlights several complicated cases involving hematologic emergencies. Dr. Shaw starts the issue with a critically ill patient in DIC. Dr. Klaszky then details a case of an arterial pseudoaneurysm. This is followed by the new "Insight from an Internist" corner where Dr. Baez describes the presentation and management of TTP. To continue the theme, pharmacy focuses on the emerging data on antiplatelet reversal in patients with intracranial hemorrhage. Moving to the abdominal pathology, Dr. Ham presents a case of cecal volvulus. In our recurring sports medicine highlight by Dr. Banning, we discuss Maisonneuve fractures to round out the blood, bowels, and bones theme for the issue. Finally, Dr. Lagasse's EKG focus features a case of neurogenic T waves.

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podcase



Disseminated
Intravascular
Coagulation



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History of Present Illness

The patient is a middle-aged female with a remote past medical history of idiopathic thrombocytopenic purpura as a teenager status post splenectomy who presents to a community emergency department (ED) with abdominal pain. She reports one day of left lower quadrant (LLQ) abdominal pain which was described as sharp, stabbing, and worsened with any movement. She has nausea but no emesis, diarrhea, constipation, or genitourinary symptoms. She is status post hysterectomy without vaginal bleeding. She has never had similar pain in the past.

Past Medical History

ITP
Hypothyroidism

Past Surgical History

Hysterectomy
Splenectomy

Medications

Levothyroxine
Multivitamin

Vitals

HR 115 BP 85/40 RR 29 O2 99% T 100.6

Physical Exam

Physical exam reveals a tearful, ill-appearing female in mild respiratory distress with some associated tachypnea. She has diffusely scattered petechiae and hemolacria (blood-tinged tears). She is tachycardic without an appreciable murmur. Her capillary refill is delayed at six seconds. Pulmonary exam reveals bibasilar crackles. Her abdomen is tender in the LLQ without rebound or guarding. Her extremities are cold, and her pulses are weak throughout. Neurologic examination is grossly intact without focal deficits.

Labs

- VBG: pH 7.15 / PCO2 47 / PO2 28 / BE -12.1
- Lactate: 15.00
- CBC 9.6/16.5/49.3/Platelets detected only in clumps
- BMP: 139/3.3/95/15/28/2.87/48
- LFT: AP 195 AST 179 ALT 93 Albumin 3.6 Bili I 1.1 Bili T 1.9 Bili D 0.8
- INR 2.5
- PTT 145.5 s
- D-Dimer >20.00
- Fibrinogen 61 mg/dL
- Urine - High protein, 2 RBC, 3 WBC, neg ketones

Imaging

- Chest x-ray- Bibasilar opacification
- CT Chest- Groundglass opacification of dependent portions of upper and lower lobes concerning for pulmonary hemorrhage
- CT Abd/Pelvis- Retroperitoneal stranding around bilateral adrenal glands concerning for adrenal hemorrhage

Hospital Course

The patient was evaluated and treated promptly and aggressively given signs of both septic shock as well as disseminated intravascular coagulation (DIC). She was given broad spectrum antibiotics with cefepime and vancomycin. In addition, she was resuscitated with three liters of intravenous fluids in the ED. Nonetheless, her metabolic acidosis worsened and she remained hypotensive. Given her refractory hypotension, a right femoral central line was placed and a norepinephrine drip was started. She received a dextrose bolus and was treated with dextrose containing maintenance fluids for her hypoglycemia. Her respiratory status slowly worsened in the ED so she was intubated for expected clinical course given her profound acidosis. CT scan revealed pulmonary as well as adrenal hemorrhage concerning for Waterhouse-Friderichsen syndrome, a syndrome characterized by severe DIC with adrenal hemorrhage often associated with meningococemia. Given refractory hypotension, hypoglycemia, and likely adrenal insufficiency secondary to hemorrhage, she was also treated with stress dose steroids. Ultimately, she was transferred to the medical intensive care unit and had a complicated, prolonged hospital course. The cause of her profound sepsis was found to be *streptococcus pneumoniae* bacteremia.

Discussion

Disseminated intravascular coagulation is a disorder of simultaneous systemic activation of coagulation and fibrinolysis, which can lead to both microvascular thrombi as well as hemorrhage. This can quickly lead to multi-system organ dysfunction, as seen in the above patient. DIC is not a primary illness, but rather secondary to a clinical condition involving systemic inflammation, with sepsis, malignancy, or trauma being the most common causes.¹ Other less common causes of DIC include heat stroke, crush injuries, vascular abnormalities, crotalid envenomation, ABO incompatibility, preeclampsia, and fat embolism. Sepsis, trauma, surgery, and solid organ malignancy each make up approximately 20% of cases of DIC.² However, this is a

relatively uncommon illness, seen in only 1% of total admissions in a retrospective, observational study of over 100,000 patients.³ While meningococemia is the most common cause of DIC leading to Waterhouse-Friderichsen syndrome in adults, *pseudomonas aeruginosa* was found to be the most common pathogen in children.⁴ Additionally, there have been reports of DIC secondary to *streptococcus pneumoniae*, *neisseria gonorrhoeae*, *escherichia coli*, *haemophilus influenzae*, and *staphylococcus aureus*.

Regardless of the cause, DIC results from diffuse activation of coagulation and fibrinolysis. This is typically triggered by exposure of tissue factor, a potent activator of the clotting cascade, to the systemic circulation. This may be in response to massive cytokine release, as in sepsis, or from direct vascular damage from trauma or surgery. Because of the underlying illness, there is a lack of localization and regulation of coagulation which results in systemic activation of the clotting cascade. This leads to diffuse microvascular thrombosis which can compromise perfusion and lead to organ dysfunction. As clotting factors are consumed, the process can lead to concomitant bleeding, making treatment particularly complicated.

The diagnosis of DIC is often suspected clinically and confirmed with laboratory data. All patients with evidence of severe systemic illness and shock in addition to physical exam findings suggestive of coagulopathy should be evaluated for DIC. Patients in the ED will typically be in the acute, decompensated phase of illness. Therefore, they will most commonly present with findings of increased bleeding. Providers should have a high index of suspicion for DIC in patients with ongoing oozing from trauma and procedure sites, petechiae, purpura, sig-

nificant bruising, or refractory epistaxis. Often, severe bleeding can even be seen from simple peripheral line placement. In addition, these patients will likely display signs of shock, including but not limited to decreased capillary refill, cool extremities, altered mental status, tachypnea, or tachycardia.

Given that DIC occurs secondarily to another illness, a careful history and exam is crucial to identification and management. Providers should elicit any infectious symptoms that could result in sepsis, recent traumatic injuries, and current or prior cancer history. If a cause is not readily apparent, further questioning is required as treatment is centered around identification of the underlying disorder.

To confirm the diagnosis of DIC, emergency providers should order laboratory studies that highlight the underlying pathophysiology of the illness. In DIC, the coagulation cascade is activated but unregulated. The unregulated clotting cascade causes microthrombi that are formed by cleavage of fibrinogen into fibrin to form platelet/fibrin clots. This process consumes the body's coagulation factors, and with a lack of platelets or coagulation factors, the intrinsic and extrinsic coagulation cascades are unable to control bleeding.¹ Therefore, studies obtained at the initial presentation in the emergency department should evaluate for fibrinolysis with "fibrin split products." These include fibrinogen levels, D-dimer, prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT). A complete blood count (CBC) should be sent to evaluate for anemia and thrombocytopenia, as well as a peripheral smear to evaluate for evidence of microangiopathic hemolytic anemia. Figure 1 shows what these lab tests will typically reveal in acute, decompensated DIC.

The International Society for Thrombosis and Haemostasis Subcommittee recognizes a published scoring system to help identify DIC (Figure 2).⁵ In order to utilize this score, the patient must have an identified underlying disorder that is known to be associated with DIC as

Laboratory Findings in Acute DIC	
- Platelet Count	↓
- Fibrinogen	↓
- PT (INR)	↑
- PTT	↑
- D-dimer	↑
- Peripheral smear	Schistocytes, helmet cells

Figure 1: Laboratory findings in DIC

CONTINUED ON PAGE 14

Ulnar Artery



PSEUDOANEURYSM

Michael Klaszky, MD

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History of Present Illness

The patient is a male in his 30s who presented to the emergency department (ED) via police escort with a right arm laceration and suicidal ideation. The patient was in an argument with several family members just prior to presentation, and in frustration drove his fist through a glass window. Upon presentation, he was complaining of pain in his right arm but denied numbness, paresthesia, and weakness in the right hand.

mattress sutures and one simple interrupted suture with good approximation and cosmesis. It was dressed with gauze and Kerlix, and the patient was discharged with instructions to follow up in one week for suture removal.

Past Medical History

Depression

Past Surgical History

Incision and drainage of a prior left leg gunshot wound

Medications

None

Vitals

T 98.3 HR 63 BP 135/89 RR 16 SpO2 98% in room air

Physical Exam

The patient is an African American male who appears his stated age and is in no apparent distress. He has a 3 cm linear laceration to the volar surface of the right forearm with a moderate amount of pulsatile bleeding and no obvious foreign bodies or gross contamination present. His distal ulnar and radial pulses are intact in the right wrist with a brisk capillary refill in the right fingers. He has intact sensation to light touch in the median, ulnar, and radial nerve distribution in the right hand. He also has intact motor function of the radial, median, and ulnar nerves. Cardiovascular, pulmonary, abdominal, and neurologic exams are within normal limits.

The patient returned to the ED two weeks later. At that time, he reported that the wound had been bleeding for two days and his forearm had become increasingly swollen. His repeat exam revealed a diminished ulnar pulse in his right wrist and a palpable pulse over his laceration repair. A CT angiogram of the right upper extremity revealed a 2.2 cm multilobulated pseudoaneurysm arising from the ulnar artery at the level of the proximal forearm with no active extravasation. Hand surgery was consulted and recommended placing a compression dressing over the area and to leave the sutures in place. Follow up was arranged three days later in hand clinic.

The patient was seen in hand clinic and the decision was made to repair the pseudoaneurysm operatively. He was taken to the operating room the following day and underwent pseudoaneurysm excision and primary repair of the ulnar artery with no complications. A heparin drip was started post-operatively and the patient was discharged on post-op day three with instructions to take a full dose aspirin twice daily.

Labs and Imaging

Na 140 K 3.9 CO2 32 Cr 0.96 Glu 107
ETOH 241

Urine drug screen negative

X-ray Right Radius/Ulna: No acute osseous findings of the right forearm. Large soft tissue edema without visible radiopaque foreign body.

Hospital Course

The patient presented with a simple laceration and what appeared to be a small, superficial arterial injury to the right forearm. Hemostasis was achieved quickly with compression over the injury, and the wound was irrigated with saline. The wound was repaired with two horizontal

Discussion

An aneurysm is defined as a localized dilation of an artery to at least 1.5 times its normal diameter. A true aneurysm involves dilatation of all three layers of the vessel wall: the intima, media, and adventitia. A false aneurysm, or pseudoaneurysm, is similar but does not include all layers of the arterial wall. Pseudoaneurysms may be confused with a pulsatile hematoma, which often occurs during traumatic injury to the blood vessel.¹

The most common cause of pseudoaneurysm formation is secondary to catheterization for either angiography or cardiac catheterization, and they are most commonly found in the femoral artery. Meanwhile, true aneurysms are most commonly found in the infrarenal abdominal aorta, as well as the iliac, femoral, and popliteal arteries.¹

Aneurysms and pseudoaneurysms are much less frequently encountered in the upper extremities, as in the case described above. Despite the low overall incidence of upper extremity pseudoaneurysms, several case reports have been published describing pseudoaneurysm formation following traumatic injury to the affected artery. Cases have been reported following self-inflicted injuries,

blast injuries during combat situations, and injection drug use.^{2,3} Pseudoaneurysms can also form in vascular access sites of hemodialysis patients, most frequently occurring with AV grafts. These pseudoaneurysms commonly form after repeated vascular access from the same site, and the incidence of pseudoaneurysms in AV grafts increases with the age of the graft.⁴

Aneurysms commonly form in atherosclerotic arteries as a mechanism to bypass an area of decreased arterial flow. True aneurysms typically take longer periods of time to develop, on the scale of months to years. Pseudoaneurysms, on the other hand, often develop rapidly following an injury to the affected artery that results in disruption of the vessel wall without complete rupture.⁵ The area of the artery that sustained trauma is replaced by an organized hematoma with a fibrous wall resulting in localized dilatation of the vessel.

Patients will often report a slow growing or painful mass. Many will experience sensory disturbances in a dermatomal distribution if the aneurysm is compressing a nearby nerve. On physical exam, the provider will often be able to palpate a mass, which is only pulsatile in about 50% of cases.⁵

There may also be changes in the overlying tissue, such as local erythema, eschar formation, skin necrosis, or erosion. A history of preceding trauma, intravenous drug use, or intermittent hemodialysis access to the area should prompt consideration of this diagnosis.

The differential diagnosis for a patient presenting with a slowly expanding and painful mass is fairly broad, and will often require advanced imaging to make a definitive diagnosis. Other than pseudoaneurysm, clinicians must also consider other vascular abnormalities such as true aneurysm, arterial fistula, and expanding hematoma. Infectious causes such as abscess or infected hematoma can present similarly, often with overlying cellulitis and warmth. Inflammatory causes such as vasculitis can also present similarly,

although this would likely present as a more chronic rather than acute problem. A foreign body with granuloma formation can present similarly, and should be considered especially if a penetrating injury occurred, such as a laceration with glass, metal, or wood. Finally, neoplastic causes should also be considered, such as angio- ma, neuroma, and soft tissue lipoma.

Laboratory testing is not necessary in making the diagnosis of pseudoaneurysm. However, studies such as a complete blood count, sedimentation rate, and c-reactive protein can be helpful for consultants, especially if the pseudoaneurysm will be

has not been studied extensively at other sites and is operator dependent. Regardless, it remains a viable option when evaluating these lesions.

While traditional angiography remains the “gold standard” for this diagnosis, with advances in CT technology, CT angiography has become an extremely valuable tool in the diagnosis of pseudoaneurysms. CT angiography can be obtained quickly and is useful for surgical planning. CT angiography can also detect alternative diagnoses and injuries, as well as give information on blood flow to the pseudoaneurysm. It can also detect active extravasation from the pseudoaneurysm.⁸ CT angiography has been reported to have a sensitivity of 95.1% and specificity of 98.7% in detecting pseudoaneurysms in the proximal extremities, making it an excellent diagnostic study that can be obtained in the ED.⁹

MRI is another imaging modality that can be used in diagnosing pseudoaneurysms. While MRI does not expose the patient to ionizing radiation or iodinated contrast, it is a time- and resource-intensive test that requires patient cooperation. The sensitivity and specificity in detecting pseudoaneurysms are similar to that of CT angiography, making it an effective diagnostic tool. Nonetheless, the time required to obtain this study is often a limiting factor.

Once the diagnosis has been made with advanced imaging, surgical consultation is warranted. If there are no signs of extravasation on imaging and the patient is hemodynamically stable, operative planning can often be arranged as an outpatient. However, more urgent surgical intervention is indicated if there is active extravasation, significant erosion of the overlying skin, evidence of infection, or signs of compartment syndrome of the affected extremity.⁴

Emergency physicians must have a low threshold for advanced imaging if this diagnosis is suspected, as the consequences of a missed diagnosis are severe and can be limb threatening. Failure to

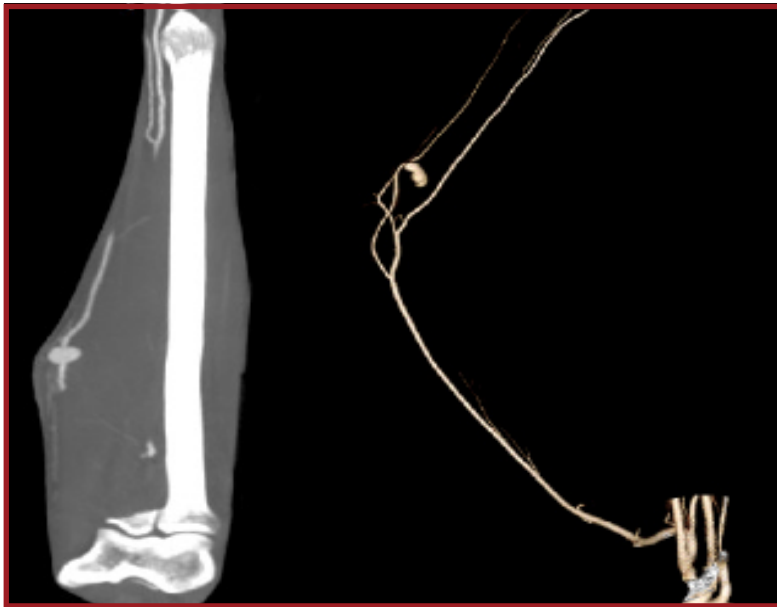


Figure 1: Left: CTA imaging revealing a large ulnar artery pseudoaneurysm. Right: 3D rendering of the patient's pseudoaneurysm.

managed surgically. The diagnosis is confirmed by imaging, and several different modalities can be used.

Doppler ultrasound is a useful study that does not subject the patient to any contrast or radiation, and it can be performed quickly at the bedside. The pseudoaneurysm will appear as a hypoechoic cystic structure adjacent to the artery.⁶ Color doppler may show the classic “yin-yang sign” which is a swirling, alternating color motion within the aneurysm.⁷ The most specific ultrasound finding for a pseudoaneurysm is a communicating channel between the artery and sac with a “to and fro” waveform on duplex ultrasound.⁸ Ultrasound has been reported to have a sensitivity of 94% with a specificity of 97% in detecting pseudoaneurysms of the femoral artery after cardiac catheterization, but it

CONTINUED ON PAGE 13

Insight from an Internist: TTP

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Chief Medicine Resident



History of Present Illness

The patient is a female in her 50s who presents with abdominal pain for one month prior to presentation. Her symptoms were initially intermittent but have been constant for the past week. Her pain starts in the epigastrium and radiates to the bilateral lower quadrants. It is sharp and severe with no modifying factors. Associated symptoms include decreased appetite and nausea without emesis. She endorses intermittent chronic non-bloody diarrhea but her bowel movements for the past week are normal and formed. She has seen her primary physician for these symptoms who prescribed a proton pump inhibitor and ondansetron without relief. She has been referred to a gastroenterologist but has not yet had her appointment.

Past Medical History

Hypertension
CAD
AAA

Past Surgical History

Cholecystectomy

Medications

ASA	Lisinopril	Omeprazole
Metoprolol tartrate	Atorvastatin	Ondansetron

Vitals

T 98.3 BP 127/79 HR 84 RR 17 98% on RA

Physical Exam

The patient is alert and overall non-toxic appearing despite looking mildly uncomfortable. Oropharynx is moist without any intra-oral lesions or gingival abnormalities. Abdominal exam reveals a soft abdomen with normal bowel sounds. Palpation elicits epigastric and bilateral lower quadrant tenderness without guarding or rebound. Cardiac, pulmonary, and neurologic examinations are all within normal limits. Skin exam is without rash, bruising, or petechiae.

Labs and Imaging

WBC 10.5, Hg 13.7
PLT $9 \times 10^9/L$
BMP normal
Total bilirubin 1.7, Indirect bilirubin 1.4, LDH 888
INR 1.1, PT 13.9

CT A/P with contrast: No acute abnormality in the abdomen or pelvis. 3.1 x 3.6 cm infrarenal abdominal aortic aneurysm. Borderline splenomegaly.

Hospital Course

The patient was admitted to medicine with abdominal pain, mild anemia with indirect hyperbilirubinemia, and severe thrombocytopenia concerning for an acute microangiopathic process. Hematology was consulted from the emergency department, evaluated the patient, and recommended a peripheral smear. The smear demonstrated one to two schistocytes per high-powered field, less than the diagnostic cut-off suggestive of thrombotic thrombocytopenic purpura (TTP). Given the concern for possible idiopathic thrombocytopenic purpura (ITP), omeprazole was discontinued due to its risk of drug-induced ITP. Hemolysis labs including complete blood count (CBC), lactate dehydrogenase (LDH), haptoglobin, and bilirubin levels were trended. On hospital day one, the patient's repeat platelet count was $15 \times 10^9/L$ and her hemoglobin had dropped by two grams. Based on the newly derived PLASMIC score (see below), the patient had a high positive predictive value for TTP associated with severe ADAMTS13 deficiency. Therefore, treatment for acute TTP was initiated with daily plasma exchange and high dose prednisone. The patient tolerated plasma exchange therapy well. After each round of therapy her platelet count and evidence of hemolysis gradually improved. After two sessions, her abdominal symptoms resolved. After three sessions, her laboratory studies normalized. The ADAMTS13 activity level returned at less than 2% confirming the suspected diagnosis of TTP. On the day of discharge her platelets had improved to $293 \times 10^9/L$ and she had no further evidence of hemolysis. The patient was discharged on prednisone 60mg daily with plans for outpatient plasma exchange and hematology follow-up.

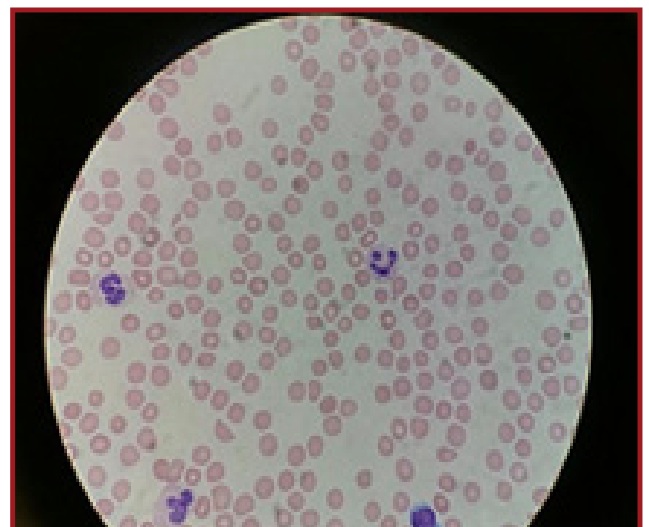


Figure 1: Patient's initial peripheral smear with 1-2 schistocytes/hpf

Discussion

TTP is a rare, life-threatening primary thrombotic microangiopathy caused by functional or intrinsic deficiency of the von Willebrand factor (vWF) cleaving protein ADAMTS13. This results in severe thrombocytopenia, microangiopathic hemolytic anemia, and multi-organ injury. ADAMTS13 deficiency comes in two forms. The first is an acquired mechanism via immune-mediated autoantibodies against ADAMTS13. The second is an inherited mechanism via mutations of the ADAMTS13 gene called Upshaw-Schulman syndrome. The estimated annual incidence of acquired TTP is 2.88 per million persons whereas the estimated annual incidence of inherited TTP is less than one per million persons.¹ The subsequent discussion will focus on acquired TTP as it is more likely to present for the first time as an adult (90 percent of cases) and is associated with other more common conditions.¹

The only known risk factor for developing TTP is severe ADAMTS13 deficiency. ADAMTS13 is a protein that cleaves vWF, which is a glycoprotein secreted by endothelial cells to support platelet adhesion. It elongates within high shear stress environments and enables platelet aggregation. Intermittent shear stress events naturally elongate vWF in normal physiologic conditions. This opens ADAMTS13 cleavage sites and allows the ADAMTS13 protein to cleave and inactivate vWF. This helps regulate platelet aggregation. Decreased ADAMTS13 protein activity results in increased levels of abnormally large, sticky vWF multimers. Platelets then spontaneously aggregate leading to widespread formation of microvascular microthrombi. Platelets are consumed within these thrombi resulting in thrombocytopenia. Red blood cells are lysed by microthrombi causing a microangiopathic hemolytic anemia (figure 2).²

Patients with TTP clinically present on a spectrum ranging from nearly asymptomatic to critically ill. The historical pentad of fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms, and renal failure has been shown through

several cohort studies to exist in less than 10 percent of acute TTP cases.^{1,3} Typical presenting signs and symptoms include a combination of microangiopathic hemolytic anemia (jaundice and fatigue with median hemoglobin 8-10 g/dL), thrombocytopenia (petechiae and mucosal bleeding with platelets $<30 \times 10^9/L$), and multi-system organ dysfunction. The central nervous system is primarily affected in TTP, but all organs can be involved. This makes differentiating between TTP and other thrombotic microangiopathies (*e.g.*, hemolytic uremic syndrome) quite difficult. About 60 percent of patients have neurologic symptoms at presentation ranging from headache to seizures. Patients often present with GI symptoms like abdominal pain and diarrhea, due

department, providers should suspect acquired TTP in adults with severe thrombocytopenia and microangiopathic hemolytic anemia. This is suggested by indirect hyperbilirubinemia and elevated LDH. TTP should also be suspected in the setting of more commonly associated conditions such as SLE, pregnancy, HIV, malignancy, and organ transplantation. TTP should also be considered in patients with new neurological symptoms or acute myocardial infarction with unexplained thrombocytopenia and hemolytic anemia.

In cases of suspected TTP, additional testing to assess for the presence and extent of end-organ damage is indicated. Because patients are at risk for microvascular thrombotic events, providers should obtain laboratory testing to evaluate for coagulopathy, renal dysfunction, cardiac ischemia, and neurologic sequelae. In uncomplicated cases of TTP, standard coagulation parameters are typically unaffected. Renal assessment is usually normal but can demonstrate elevated serum urea and creatinine levels. Urinalysis may show proteinuria and/or hematuria. A troponin level greater than 0.1 $\mu\text{g/L}$ is present in up to 60 percent of cases, although the majority of patients have no clinical cardiac involvement. Repolarization changes on electrocardiogram are present in 10 percent of cases.⁴

Emergency department management includes urgent hematology-oncology consultation and obtaining a peripheral blood smear. In 2012, the International Council for Standardization in Hematology (ICSH) systematized the identification and diagnostic merit of schistocytes. According to the ICSH published guidelines, greater than 1 percent schistocytes or roughly four per high powered field in the absence of other significant red blood cell changes suggests thrombotic microangiopathy.⁶ Measurement of ADAMTS13 activity is the only specific confirmatory diagnostic test, but will not result during an ED visit and should be ordered in consultation with a specialist. Treatment should not be delayed while waiting for ADAMTS13 activ-

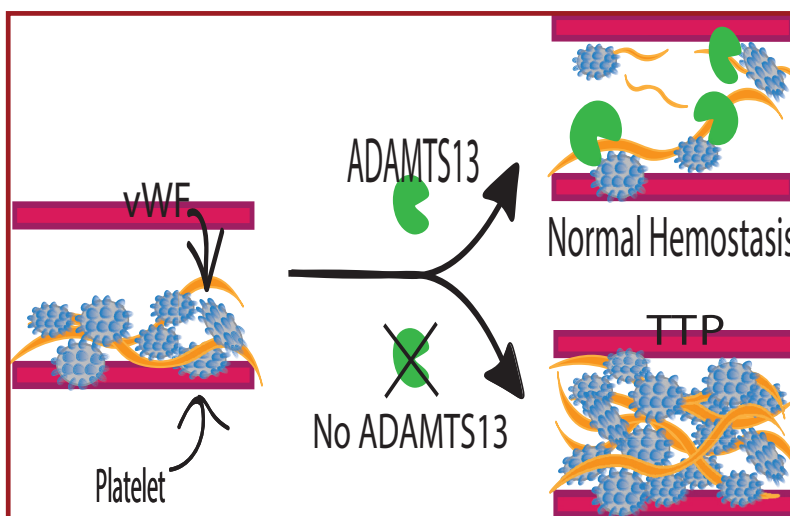


Figure 2: Function of ADAMTS13

to the mesenteric ischemia which occurs in approximately 35 percent of cases. The cardiovascular system is affected in about 25 percent of cases, ranging from isolated ECG abnormalities to myocardial infarction. Acute renal failure is seen in approximately 27 percent of cases.¹

About 50 percent of patients with TTP may have another concomitant or preexisting clinical condition. The most frequently associated conditions are bacterial infections, autoimmune diseases (*e.g.*, systemic lupus erythematosus [SLE]), pregnancy, drugs (notably cyclosporine and clopidogrel), HIV infection, malignancy, and organ transplantation. It is thought that these concomitant conditions may be the triggering mechanism for a TTP episode.¹

Early detection and diagnosis of TTP is vital to initiate appropriate treatment and limit morbidity and mortality. In the emergency

CONTINUED ON PAGE 14

ANTIPLATELET REVERSAL IN Intracerebral Hemorrhage

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Edited by: Maddy Foertsch, PharmD and Nicole Harger, PharmD, BCPS, BCCP

Spontaneous intracerebral hemorrhage (ICH) is a stroke subtype that is associated with significant morbidity and mortality. About 50% of all patients with ICH die within the first month of the event, and only about 20% of patients live independently six months post-hemorrhage. Patients who have expansion of their hematoma have been shown to have worse outcomes, making prevention and limitation of hematoma expansion of the utmost importance.¹

Multiple classes of antiplatelet agents exist, including cyclooxygenase inhibitors, adenosine diphosphate receptor inhibitors, phosphodiesterase inhibitors, glycoprotein IIB/IIIA antagonists, and protease-activated receptor-1 antagonists (Table 1). These agents can be further classified as having either reversible or irreversible antiplatelet activity. In general, antiplatelet agents that work through ADP inhibition are more potent in their antiplatelet effects than those that work through COX-inhibition.

Theoretically, the use of antiplatelet drugs increases risk of ICH, hematoma expansion, and poor neurologic outcome. However, current literature on this topic is controversial. One pooled analysis of 14 randomized trials which included 27,889 patients found no difference in the rate of ICH in patients receiving heparin with a concomitant glycoprotein IIB/IIIA inhibitor versus heparin alone.² Additionally, a cohort analysis of 282 patients from the prospective Cerebral Hemorrhage and NXY-049 (CHANT) trial found that the use of antiplatelet medications at ICH onset has no association with the volume of ICH at presentation, growth of the hematoma at 72 hours, modified Rankin score at 90 days, initial hematoma volume, or increase in cerebral edema.¹ However, another trial found worse outcomes in patients with ICH on antiplatelet agents, including hematoma expansion.³ This uncertainty about the impact of antiplatelet use on negative outcomes in patients with ICH leads to an unclear role of antiplatelet reversal in patients presenting with an intracranial bleed.

Drug Name	Mechanism of Action	Reversible?	Duration of Antiplatelet Effect
Aspirin	COX-1 and 2 enzyme inhibitor	No	Lifespan of platelets (5-20 days)
NSAIDs (Ibuprofen, naproxen, meloxicam, ketorolac, etc.)	COX-1 and 2 enzyme inhibitor	Yes	3-5 half-lives (10 hours to several days, depending on agent)
Dipyridamole (Persantine)	Adenosine reuptake inhibitor	Yes	36-60 hours
Clopidogrel (Plavix)	P2Y12 ADP receptor inhibitor	No	Lifespan of platelets (5-20 days)
Prasugrel (Effient)	P2Y12 ADP receptor inhibitor	No	Lifespan of platelets (5-20 days)
Ticagrelor (Brilinta)	P2Y12 ADP receptor inhibitor	Yes	Peak effect: 2-8 hours, 58% effect at 24 hours
Cangrelor (Kengreal)	P2Y12 ADP receptor inhibitor	Yes	18-30 minutes
Eptifibatide (Integrilin)	GP IIB/IIIA antagonist	Yes	7.5-12.5 hours

Table 1. Summary of Common Antiplatelet Agents
NSAIDs: nonsteroidal non-inflammatory drugs; COX: cyclooxygenase; ADP (adenosine diphosphate); GP: Glycoprotein

Different platelet function assays have been utilized to detect degree of platelet inhibition by specific medications. Light transmission aggregometry is considered the gold standard for determining platelet function, but data have shown correlation between this more expensive and time-consuming process and other platelet function assays, such as VerifyNow.⁴ VerifyNow is a point-of-care test that utilizes optical detection to determine the ability of platelets to bind fibrinogen. It can be used to determine degree of inhibition by aspirin, P2Y12 inhibitors, and GP IIB/IIIa inhibitors. Values are presented as antiplatelet effect, with lower numbers indicating more antiplatelet activity. However, the available data for cut-off points and whether the tests significantly predict bleeding events is controversial and should be interpreted in conjunction with the clinical status of the patient.⁵

Platelet Transfusions

Reversible antiplatelet agents should have a clearing of effect once the drug has been held for 3-5 half-lives; however, with non-reversible agents, effects will remain until new platelets are created within the bone marrow (Table 1). The average life span of a platelet is between 8-20 days. If electing to transfuse platelets, it is important to remember that transfused platelets have a shorter half-life depending on how long they have been stored. Risks of platelet transfusion include transmission of infectious disease, transfusion reactions, transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), thrombosis, and disseminated intravascular coagulation (DIC).

The first published randomized controlled trial that looked at platelet transfusions was in patients taking aspirin who were considered “aspirin sensitive” via platelet function tests. This prospective, double-blind, parallel, randomized controlled trial included 780 patients with acute hypertensive basal ganglia hemorrhages who underwent a craniotomy and subsequent hematoma evacuation. Patients were randomized to 0, 1, or 2 pooled packs of platelets prior to surgery and it was found that those who received platelets had mortality benefit over those who did not (15.5% vs 34.2%, $p = 0.002$), as well as smaller post-operative hematomas when compared to the control group (35 vs 57 cm, $p = 0.001$).⁶ It should be noted that this study did not evaluate patients receiving other antiplatelet agents, so this data cannot necessarily be extrapolated to other populations.

Most recently the PATCH trial was completed. This was a multi-center, randomized controlled trial comparing platelet transfusion within six hours to standard of care in patients with spontaneous ICH on aspirin, dipyridamole, and/or clopidogrel. This study enrolled 200 patients and found an increased incidence of mortality and incidence of adverse events in patients who received platelet transfusions versus those who did not (adjusted common odds ratio 2.05, 95% CI 1.18–3.56, $p=0.0114$).⁷

Desmopressin (DDAVP) is a vasopressin analog that increases release of endothelial von Willebrand factor. It has been shown to reduce bleeding and increase platelet function in cardiac surgery patients who have been exposed to aspirin.⁸ Adverse events associated with desmopressin include facial flushing, peripheral edema, hypervolemia, hyponatremia, decreased urine output, and, rarely, thrombosis.⁹ This medication has been shown to improve platelet function and hemostasis in patients with uremia-induced platelet dysfunction regardless of concomitant aspirin use. One observational study enrolled 14 patients with ICH who had evidence of platelet dysfunction based on POC testing, known aspirin use, or both. Patients received a one-time dose of desmopressin (0.4 mcg/kg IV) within 12 hours of their symptom onset. Patients were found to have mean improvement in POC testing numbers at one hour and only two patients had hematoma growth. Additionally, one large, retrospective study that included 408 patients assessed hematoma expansion and mortality in traumatic ICH patients receiving platelet transfusions plus or minus DDAVP. No difference was found between the two groups.¹⁰ No large, randomized controlled trials have been conducted to assess safety and efficacy of desmopressin for the indication of ICH.¹¹

Summary

In summary, few large, randomized controlled trials assess the reversal of antiplatelet agents in patients with ICH. The Neurocritical Care Society and Society of Critical Care Medicine Guidelines recommend platelet transfusion in patients who present with ICH; however, this recommendation was issued prior to the publication of the PATCH trial, which directly contradicted the results of the previously published trial. The guidelines also state that desmopressin may be used in addition to platelet transfusion in this population.¹² Due to a lack of solid evidence and mixed outcomes amongst trials, the role of desmopressin and platelet transfusions in the formation and expansion of these bleeds remains controversial.

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Cecal Volvulus

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History of Present Illness

The patient is a female in her 30s with a past medical history of prior cholecystectomy and gastric bypass who presented with epigastric pain and vomiting following an alleged domestic assault. The incident reportedly occurred approximately 18 hours prior to coming to the emergency department (ED). The patient reported being struck by her male companion with fists in her left side, hip, and chest. On the day of presentation, she had several episodes of bloody emesis and continued to endorse uncontrollable vomiting on arrival. She described moderate epigastric pain without radiation. Her last bowel movement was the day of presentation and was described as hard but non-bloody. She denied any other associated symptoms.

Past Medical History

Intravenous (IV)
 drug abuse

Past Surgical History

Cholecystectomy
 Gastric bypass

Medications

None

Vitals

T 98.4 HR 81 BP 153/90 RR 18 SpO2 99% RA

Physical Exam

The patient was an alert, well-developed female who appeared her stated age and was in a significant amount of distress due to ongoing vomiting during the exam. Her abdominal exam was significant for a tender mass in the epigastrium that could not be reduced due to pain. There were no peritoneal signs. Cardiopulmonary and neurologic examinations were unremarkable.

Imaging

A CT of the abdomen and pelvis with oral and IV contrast was performed for vomiting, pain, and concern for new hernia. This demonstrated a whirled appearance of the mesenteric vasculature and right lower quadrant bowel loops with displacement of the cecum. There was associated mild distension of the proximal bowel loops, but no signs of pneumatosis or ectopic bowel gas. Labs, including serum lactic acid and electrolytes, were largely unremarkable.

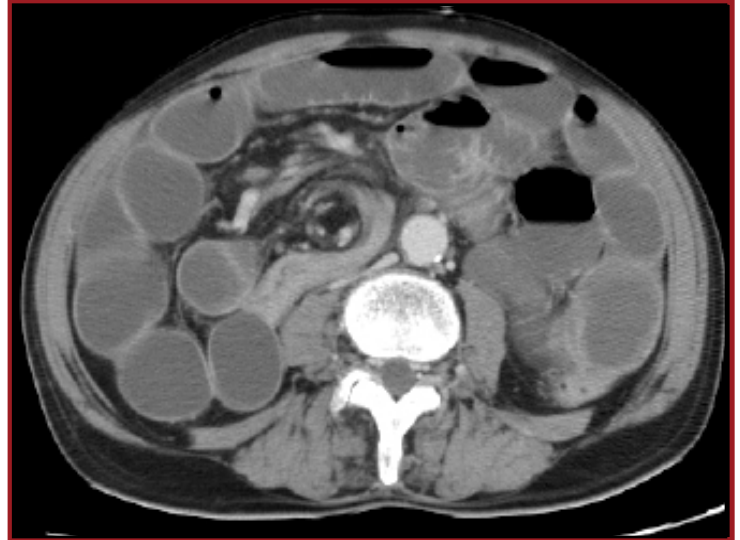


Figure 1: Representative image demonstrating the "whirl sign" seen in patients with volvulus.⁴

Hospital Course

Despite aggressive attempts at control with anti-emetics, the patient's vomiting was intractable. Based on history and physical exam, there was initially concern for a new hernia, with or without incarceration, or other obstructive bowel pathology secondary to adhesions or volvulus. Although labs did not show significant leukocytosis, acidosis, or hypokalemia from vomiting, CT imaging showed the findings as described above that were concerning for cecal volvulus. Surgery was consulted for operative management. She was started on prophylactic antibiotics with piperacillin/tazobactam and was treated symptomatically with intravenous pain and nausea medications.

In the operating room, the patient underwent an exploratory laparotomy with lysis of adhesions and a right hemicolectomy with ileocolonic anastomosis. She was symptomatically improved and was ambulating by post-operative day one, had return of bowel function on post-operative day five, and was discharged home with a bowel regimen one week after presentation.

Discussion

Cecal volvulus is a type of colonic obstruction that results from a mobile cecum that twists or folds about its associated mesentery. The mobility can be congenital or acquired, but overall these account for 1-3% of large bowel obstructions annually.¹ In the above patient, her history of abdominal surgery with formation of adhesions likely established a fulcrum for rotation. Of the subset of obstructions due to volvulus, the cecum and sigmoid colon are the two most common sites, with the former being more common in younger females (as demonstrated above) and the

latter seen more frequently in older males.

There are three types of cecal volvulus.² A type I volvulus, or axial volvulus, occurs when the cecum and ascending colon twists along the long axis, usually in a clockwise direction, and the cecum generally remains in its correct anatomic location in the right lower quadrant. A type II, or loop volvulus occurs when the cecum and terminal ileum twist usually in a counterclockwise direction and end up in an ectopic location, often the left upper quadrant. This subtype seems consistent with what occurred in the patient described above. A type III volvulus, or cecal bascule, results from an upward folding rather than twisting of the cecum. Types I and II combined account for about 80% of cecal volvuli.



Figure 2: "Coffee bean" sign seen on plain films obtained in cecal volvulus.⁵

Left untreated, cecal volvulus progresses to bowel ischemia, necrosis, perforation, and can be fatal. However, with early detection and definitive surgical management, outcomes are much more favorable.

Cecal volvulus can present with a spectrum of signs and symptoms depending on the time since onset. Generally, patients will exhibit some constellation of abdominal pain, nausea, and vomiting. Most patients will report obstipation, but lack of this symptom does not preclude the diagnosis, as demonstrated in the above case. Often, patients will have a non-focal abdominal exam and unremarkable vital signs early in the disease process. Localized abdominal tenderness is variable. For example, the tender mass appreciated in the case above likely represented the displaced cecum translocated from its anatomic home in the right lower quadrant. If sufficient time has passed for ischemia, necrosis, or perforation to occur, patients may appear septic with an acute abdomen. Overall, presentation is highly variable and requires a high index of suspicion.

In general, this diagnosis will be made with imaging. While labs may be supportive (e.g. nonspecific leukocytosis, metabolic acidosis, hypokalemia due to

protracted vomiting), none are specific enough to differentiate cecal volvulus from other abdominal pathology.

Diagnostic imaging should begin with upright abdominal films to evaluate primarily for pneumoperitoneum, but signs of large bowel obstruction may also be apparent. Particular to cecal volvulus is the classic "coffee bean" cecum, present in up to 25% of cases, and is usually seen displaced superiorly and medially. When there is no evidence of pneumoperitoneum on the upright film, the next step should be to obtain CT imaging to confirm the diagnosis.³ In very well appearing patients with a low suspicion for perforation, the decision can be made to forego the upright plain film. CT findings include the "whirl sign" which is pathognomonic for cecal volvulus. Although not routine, a barium enema can be included to further assess such patients and can reveal a classic finding of the "bird's beak" in the right colon. This represents narrowing of the volvulus segment. Furthermore, complete obstruction is suspected by an "X marks the spot" sign, which represents crossing loops of bowel at the site of transition.

Identification of volvulus mandates surgical and occasionally gastroenterology consultation. Colonoscopic detorsion,

while potentially beneficial for sigmoid volvulus, carries a much higher risk for perforation with cecal volvulus and may fail to detect colonic necrosis. Therefore, surgical involvement is generally indicated. Once in the operating suite, the patient may receive one of a variety of procedures ranging from cecopexy with cecostomy to right colectomy or ileocecectomy, and surgeons have an algorithmic approach to determining that end point.⁴

The focus of the emergency physician should be identification of this disease process and adequate resuscitation of these sometimes critically ill patients. Patients should receive intravenous fluids, antiemetics, and pain control. Intestinal obstruction promotes translocation of gut bacteria, so gram-negative and anaerobic antibiotic coverage is warranted. As in the presented case, antiemetics may not alleviate a patient's nausea, so nasogastric decompression may be warranted.

Bowel obstruction, such as that caused by cecal volvulus, is a pathology that emergency physicians should be expert in detecting. It is an acute, life-threatening condition where providers have an opportunity to intervene and relieve suffering. Definitive imaging and surgical consultation is essential in preventing morbidity and mortality secondary to this disease process.

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Quick Hit: Maisonneuve Fracture

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History of Present Illness

A female in her 50s presents to the emergency department (ED) complaining of left ankle pain after tripping over an extension cord in her home one day prior to presentation. She has been unable to bear weight since the injury. In the ED, she complains of severe pain to her left lateral ankle but denies weakness and numbness. She denies any other injury.

Physical Exam

The patient is well appearing and in no acute distress. Musculoskeletal exam is most notable for swelling and tenderness of the left ankle and lateral aspect of her proximal left fibula. There is no overlying ecchymosis or abrasions, and no other bony tenderness is noted. She has full strength in all left lower extremity muscle groups. The left foot is neurovascularly intact. No other abnormalities are noted on her cardiopulmonary, abdominal, or neurologic exam.

Imaging

The left ankle radiograph shows a non-displaced fracture plane extending into the medial aspect of the tibial plafond near the medial malleolus. The left knee and left tibia/fibula x-rays reveal a mildly displaced spiral type proximal fibular fracture, consistent with a Maisonneuve fracture pattern.



Figure 1: Representative image of a spiral fibular fracture which is diagnostic for Maisonneuve fracture.

Hospital Course

The patient received analgesia and was placed in a posterior short leg splint. She was instructed to remain non-weight bearing until she followed up with orthopedics in clinic. She was seen in clinic the following week, and underwent surgical repair three days later. This involved reduction of her syndesmosis and fixation utilizing two transverse screws across the distal tibio-fibular syndesmosis, as well as reduction and stabilization of the medial malleolus fracture. Her post-operative course was uneventful and full function was restored to the left ankle.

Discussion

The Maisonneuve fracture pattern is defined as a fracture of the proximal third of the fibula with disruption of the distal tibiofibular syndesmosis. It was first described by French surgeon Jules Germain Francois Maisonneuve in 1840.¹ Maisonneuve fractures account for about 1 in 20 ankle fractures, most commonly occurring in younger patients. This fracture pattern frequently occurs from a sports related injury.²

The injury is often sustained by internal rotation of the leg on a planted foot with relative external rotation of the talus within the ankle mortise. The rotating talus causes intra-articular torque, separating the distal tibia from the fibula. This results in a syndesmosis injury and disruption of the deltoid ligament holding the medial malleolus to multiple tarsal bones.² As the talus continues to rotate, forces continue up the interosseous membrane resulting in valgus and rotational stress along the proximal fibula. This results in the characteristic fracture pattern of the Maisonneuve fracture. This fracture pattern is usually associated with fractures of the medial malleolus or posterior portion of the distal tibia, as demonstrated in the above case. However, oftentimes there are no other bony abnormalities noted on x-ray. As a result, many of these fractures are missed or misdiagnosed as “ankle sprains”. This misdiagnosis can lead to disabling pain, prolonged rehabilitation, and premature arthritic changes.³

For this reason, the ipsilateral knee should also be examined in any patient who presents with ankle pain.² Classically patients will not initially report knee pain given that the fibula is a non-weight bearing bone. Often, the severity of the ankle pain distracts from the knee pain that can accompany this injury.

Physical exam findings that may suggest a syndesmotic injury include pain with external rotation and malleolar squeeze of the ankle.¹ To perform these tests, the patient should be supine or sitting. The examiner should stabilize the lower leg with one hand while maintaining ankle dorsiflexion with the other hand. External rotation of the dorsiflexed foot will result in pain over the interosseous membrane if a syndesmotic injury is present. To perform the malleolar squeeze test, the mid-calf is squeezed just above the distal tibia and fibula. It is suggestive of a syndesmotic injury if it causes pain distally at the ankle. Additionally, the peroneal nerve crosses over the fibular head making it subject to injury in a Maisonneuve fracture. Therefore, sensory deficits over the top of the foot may also raise suspicion for this type of injury.¹

Radiographs of both the ankle and ipsilateral knee should be obtained for further evaluation if this injury is suspected on physical examination. A spiral fracture pattern of the proximal fibula is diagnostic even in the setting of a normal ankle radiograph.⁴ Additionally, weight bearing x-rays should be obtained if possible. Local anesthesia with an ankle block can be utilized to obtain these views if the patient cannot tolerate this. Weight bearing x-rays often show the classic injury pattern of medial joint space narrowing between the tibia and the fibula. In some cases, a small avulsion fracture of the posterior malleolus is also identified with this fracture pattern. If weight bearing films cannot be obtained, CT and MRI can be utilized. Although CT scans better visualize the bony fragments, MRI can better visualize soft tissue injuries and may have improved detection of the ligamentous injuries associat-

ed with Maisonneuve fractures. In one study, MRI was noted to have a high sensitivity (90.0%) and high specificity (94.8%) when detecting these injuries.⁴

Patients need close follow up with orthopedic surgery in one to two weeks if any of the above radiographic findings are seen. All of these injuries require operative repair. Operative treatment involves reduction and stabilization of the ankle syndes-

mosis and repair of the deltoid ligament tear.¹ The fibular fracture itself is not usually surgically repaired. Although emergent evaluation by an orthopedist is not necessary in the ED, orthopedics should be contacted during the patient's ED visit in order to establish urgent outpatient follow-up. The patient should be placed in a posterior short leg splint in the ED and made non-weight bearing until follow-up. With timely diagnosis and appropriate operative management, patients with Maisonneuve fractures frequently have good functional outcomes, often with full recovery.

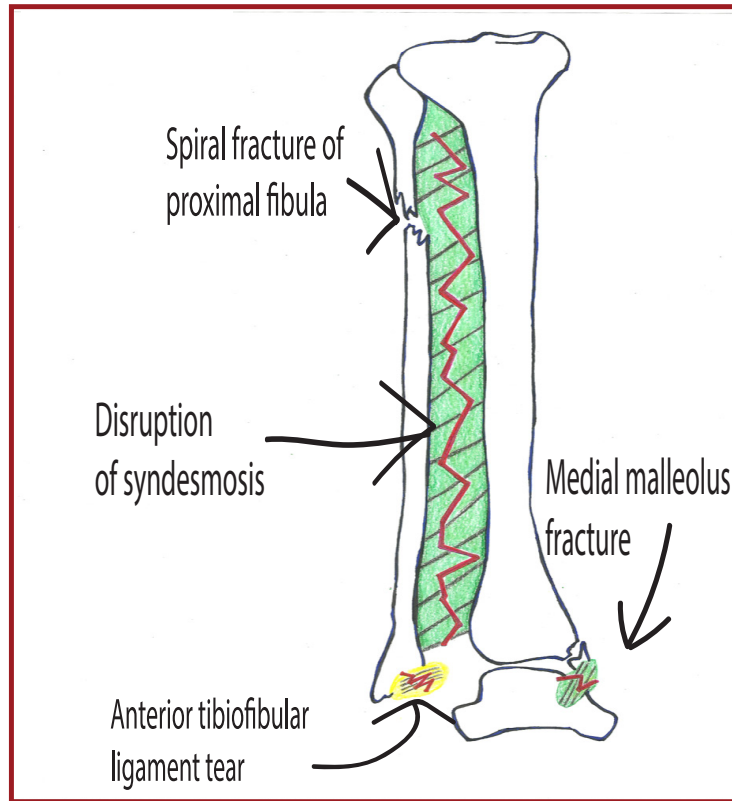


Figure 2: Components of the Maisonneuve fracture. Image drawn by Nicole Soria, MD.

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ARTERIAL PSEUDOANEURYSM
CONTINUED FROM PAGE 5

panding pseudoaneurysm and arrange surgical follow up can lead to compartment syndrome and permanent neurologic deficits.⁸

While the overall incidence of peripheral artery pseudoaneurysm is low, missing this diagnosis has severe consequences for patients and should always be considered in the evaluation of a mass in the extremity, especially in the setting of recent trauma or arterial instrumentation.

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discussed previously. The score can then be calculated by using the results of the above labs. A score of less than five is not suggestive of DIC, while a

score greater than or equal to five is indicative of overt DIC. Additionally, there is an association between higher scores and increasing mortality. This score is 91% sensitive and 97% specific for DIC and provides a way to risk stratify critical patients with higher scores.⁶

can be used to correct an elevated INR. Vitamin K should also be administered to those with active bleeding and an elevated INR.⁶ Platelet transfusion should be initiated for platelet count less than 10,000 or less than 50,000 with active bleeding. Cryoprecipitate should be transfused for fibrinogen levels less than 100 mg/dL.

If the etiology of DIC is not discovered on the history and physical examination, emergency providers should broaden the work-up to identify the principal disorder as indicated. For example, pregnancy testing should be performed in females of child-bearing age. Consideration of malignancy work-up may be warranted if suggested by the history. All patients with DIC should have blood cultures obtained due to the strong association with sepsis. Imaging is not mandatory but should be obtained if clinically indicated by the presenting symptoms, as in the previously described case.

Treatment for DIC in the ED is primarily supportive and aimed at treating the underlying illness to eliminate the stimulus for coagulopathy. These patients are often critically ill and may require an advanced airway, aggressive intravenous fluid resuscitation, and vasopressor support as needed. Frequently, broad spectrum antibiotic coverage is indicated, and this can be expanded to fungal/viral coverage based on the patient's clinical presentation. Delivery of the fetus is indicated if DIC is secondary to a pregnancy-related complication.

As DIC can increase both thrombosis as well as bleeding, use of blood products is controversial. There is a lack of evidence on when to use these, so treatment is largely based on consensus opinion. With the best available evidence, coagulopathy should be reversed in the case of active bleeding, recent trauma, or need for urgent or emergent surgery. Fresh-frozen plasma or prothrombin complex concentrate

ity to result because of the high morbidity and mortality rates associated with delayed diagnosis of TTP. Because early diagnosis and treatment is so important, a new point-based TTP scoring system has recently been developed and validated to predict an acquired ADAMTS13 deficiency.

The PLASMIC score (figure 3) is a laboratory-derived scoring system to predict TTP. The score was generated from a cohort study of 214 patients with TTP in which 29 laboratory variables were evaluated. Five independent markers were identified as highly predictive of TTP. These markers include a platelet count less than $30 \times 10^9/L$, serum creatinine level less than 2.0, INR less than 1.5, mean corpuscular volume (MCV) less than 90, and the presence of

Despite aggressive treatment, severe DIC has a mortality rate of greater than 75% which typically results from multi-system organ failure.⁷ Early recognition and aggressive resuscitation is therefore imperative in the ED. These patients should be admitted to the ICU for continued resuscitation as well as the high morbidity and mortality associated with this condition. Due to the complex nature of their coagulopathy, these patients would benefit from an early hematology consult. Additional consulting services may be indicated depending on the underlying etiology of the patient's DIC.

In summary, DIC is a pathologic activation of the coagulation cascade that can result in concomitant thrombosis and bleeding. Management of this critical illness begins in the ED, making identification and initial stabilization of such patients a crucial responsibility for emergency providers. While mortality remains high, proper ED care can help optimize patient outcomes.

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Scoring System for DIC		
Parameter	Result	Score
Platelet count	>100K	0
	<100K	1
	<50K	2
D-dimer	no increase	0
	moderate increase	2
	strong increase	3
PTT	<3sec	0
	>3sec	1
	>6sec	2
Fibrinogen	>100 mg/dl	0
	<100 mg/dl	1
Score ≥ 5 is indicative of overt DIC with increasing scores correlating with higher mortality.		

Figure 2: Scoring System for DIC based on ISTH criteria.⁵

nostic confirmation with ADAMTS13 level.⁷ Emergency providers should be familiar with this scoring system because it can easily be calculated from testing obtained in the ED and can expedite diagnosis and treatment. Nonetheless, this scoring system should be used in conjunction with an ADAMTS13 activity level. Diagnosis is ultimately confirmed by an ADAMTS13 activity of less than 10 percent.^{1,3,7,9}

Standard treatment for acute TTP is daily plasma exchange, often in conjunction with steroids. Daily plasma exchange replaces deficient ADAMTS13 and filters ADAMTS13 autoantibodies. Steroid therapy suppresses ADAMTS13 autoantibodies. Plasma exchange should be continued until the platelet count is greater than $150 \times 10^9/L$ and LDH is less than 1.5 times the upper limit of normal. Cessation of plasma exchange is determined by normalization of laboratory values in conjunction with clinical improvement.³

It is important to note that platelet transfusion is not indicated unless there is life threatening hemorrhage or if an emergent invasive procedure must be performed. While the evidence is conflicting, recent studies have shown increased risk of arterial emboli and mortality in those with TTP who received platelet transfusion.¹³ Studies have not, however, proven the traditional theory that transfusions "fuel the fire" in TTP or that transfusion is causally related to increased mortality.¹⁴ It is possible that those patients receiving platelet transfusions represent the more severely ill and therefore higher risk of mortality from the start. Regardless, it is standard practice to avoid platelet transfusions if at all possible in those with TTP.

TTP has a mortality rate of 10 to 20 percent and estimated relapse rates of 40 to 50 percent despite standard therapy.^{1,10} Factors portending worse outcomes and treatment failure include older age, LDH greater than 10 times the upper limit of normal (suggestive of worse organ damage), and troponin values greater than 0.25 ng/dL.¹ Some studies have suggested that severe ADAMTS13 deficiency during periods of remission may predict relapse without concomitant microangiopathic hemolytic anemia and thrombocytopenia. Recent studies show that immune modulators like rituximab can be considered in these instances.¹⁰

Rituximab is an anti-CD20 monoclonal antibody. It is typically reserved for refractory TTP after 30 days of treatment, relapsing TTP, or poor response to first-line therapy. Akin to steroid therapy, rituximab targets autoantibodies against ADAMTS13. Retrospective and prospective studies where rituximab was used after suboptimal response to standard therapy have yielded promising remission rates ranging from 89 to 98 percent.¹ Given these promising results, a phase 2 clinical trial showed that frontline treatment with rituximab plus plasma exchange and steroids may result in shorter hospitalization, fewer relapses, and no significant infectious or clinical adverse outcomes.⁶ Two other recent analyses have shown similar results. As such, frontline

therapy with rituximab is an emerging yet controversial treatment as it may unnecessarily expose a patient to a cytotoxic agent when that patient may respond to standard therapy alone.

PLASMIC Score		
Parameter	Result	Score
Platelet count	<30K	1
Creatinine	<2.0	1
INR	<1.5	1
MCV	<90	1
Presence of hemolysis variable	Either: -Retic > 2.5% -Undetectable haptoglobin OR -iBili > 2 mg/dL	1
Absence of active cancer		1
No prior stem cell or organ transplant		1

Figure 3: PLASMIC Score. Score 0-4: Low risk for TTP. Score 5-6: Intermediate risk, more testing needed. Score 7: High risk for TTP, can treat empirically.⁷

Emergency providers should treat TTP as a medical emergency with a goal to initiate plasma exchange within four to eight hours of initial clinical diagnosis.⁷ Treatment should not be delayed for confirmatory ADAMTS13 measurement. Plasma exchange transfusion requires placement of tri-lysis line or other hemodialysis catheter. In consultation with a hematologist, high dose steroids (oral prednisone 1mg/kg/day or IV methylprednisolone 1g/day) are often administered. If plasma exchange is not available, fresh frozen plasma may be considered as a temporizing measure to replace deficient ADAMTS13 until definitive treatment with plasma exchange becomes available.⁹ The patient should be considered for admission to an intensive care unit. After admission and standard treatment via plasma

exchange with or without steroids is initiated, serial measurement of hemolysis markers and thrombocytopenia should be monitored. The primary inpatient team should consider evaluating the patient for commonly associated conditions including HIV, pregnancy, and SLE. After complete therapeutic response, the patient should be followed by a hematologist and monitored long-term with periodic measurement of ADAMTS13 activity, even during periods of remission.

In summary, TTP is a diagnosis that can be made using simple laboratory data obtained in the ED. With the advent of the PLASMIC score, emergency providers can expedite treatment in consultation with a specialist. Standard therapy with plasma exchange and steroids leads to clinical response in most patients. Platelet transfusion should be avoided if possible. For patients who do not fully respond or relapse, rituximab should be considered. Through early recognition and treatment, emergency providers can lessen the morbidity and mortality associated with this rare disease process.

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EKG focus

Grace Lagasse, MD
University of Cincinnati R4

History of Present Illness

The patient is a male in his 60s who presented with altered mental status. The patient had a past medical history of pulmonary embolism and is anticoagulated on rivaroxaban. An EKG was concerning for deep inverted precordial T waves (Figure 1). A head CT showed a large right sided subdural hematoma and parenchymal hemorrhage associated with mass effect as seen in Figure 2. The patient ultimately went to the OR for a right sided hemicraniectomy and did not require any cardiac intervention during his hospitalization.

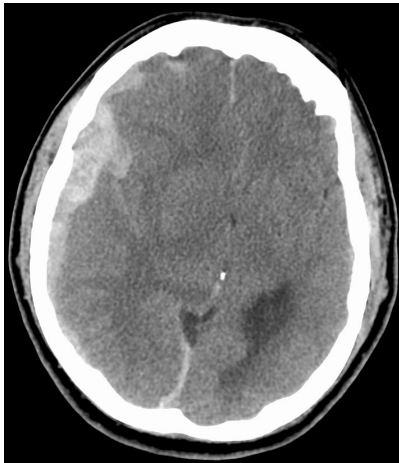


Figure 2. Representative image of the patient's head CT showing a spontaneous large right sided subdural hematoma and parenchymal hemorrhage with mass effect.

EKG and Case referred by

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Annals of B Pod is always looking for interesting cases to publish!

Please submit cases via EPIC In Basket message to Dr. David Habib. Make sure to include the R1/R4 involved in the case.

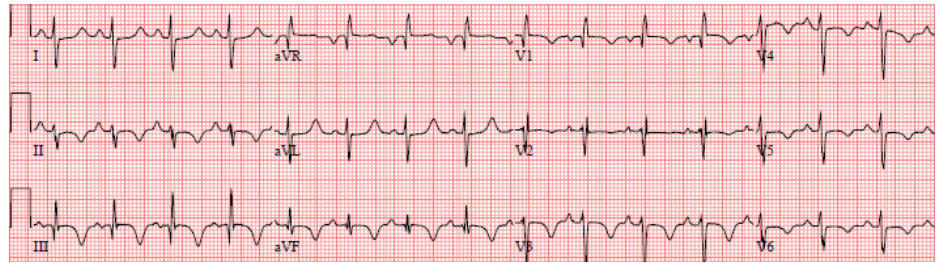


Figure 1. The patient's EKG showing classic cerebral T-waves. Note the widespread T-wave inversions associated with QTc prolongation.

Cerebral T-Waves

Cerebral T-waves are a type of EKG abnormality that may be seen in patients with acute intracranial hemorrhage (ICH). These T-waves are described as deep, symmetrical, inverted T-waves and are seen primarily in the precordial leads. It is thought that these EKG changes may be associated with increased intracranial pressure. While not diagnostic of an ICH, these T-waves have been described in up to 50% of ICH patients, and are more common with frontal lobe involvement. The etiology of these EKG changes in patients with ICH is thought to be related to alterations in the autonomic nervous system, although this remains an active area of research.

EKG Features of Cerebral T-Waves



Note the deep, symmetrical, and inverted T-waves. Cerebral T-waves are commonly found in association with a prolonged QTc. In this EKG, the QTc is >500 ms.

It has been noted that cerebral T-waves may resolve if brain death occurs and are not associated with any underlying cardiac abnormality on autopsy. As such, these EKG changes fall into the larger category of reversible EKG repolarization changes. These changes may be representative of subclinical cardiac abnormalities such as myocardial edema or of more global cardiac dysfunction such as Takotsubo cardiomyopathy.

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List of Submitted B Pod Cases

Case

Mononucleosis with amoxicillin hypersensitivity
Thyroid cartilage fracture
Hypopion
Subarachnoid hemorrhage
Lithium toxicity
ANCA glomerulonephritis
HELLP + liver hematoma
Depakote toxicity
Guillain-Barre syndrome
Acute cholangitis

Case Physicians

Golden
Lagasse
Plash
Gottula
Wood
Gleimer
Scanlon
Jensen/ Skrobut
Golden
Banning