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ANNALS OF B POD

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Spring is often the most beautiful time of year with flowers blooming, birds singing, nervous residents stepping up into their new roles, and of course incredible pathology in B pod! Join us in this issue as we review several rare cases seen by our residents this spring, as we meander through a hodge podge of urological, toxicological, and global health emergencies. We also delve into the rare but dangerous cardiac rhythms that we always think about but rarely see, and how to manage these patients when seen in the pod!

TESTICULAR TORSION

Trevor Skrobut, MD
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History of Present Illness

The patient is an 18-year-old male with a past medical history of asthma who is brought to the Emergency Department (ED) via EMS for sudden onset of sharp, severe left sided scrotal pain and swelling. The patient was suddenly awoken from sleep by the onset of left testicle pain two hours prior to arrival. The patient also reports mild abdominal pain. He states that he had spent the prior day lifting heavy objects, but denies any specific injury to his genitals. The patient was completely asymptomatic prior to this episode. He specifically denies associated dysuria, hematuria, flank pain, penile discharge, or a history of sexually transmitted infection. He is sexually monogamous with his wife.

Past Medical History
Asthma

Medications
Ibuprofen as needed for pain

Past Surgical History
None

Allergies
None

Physical Exam

Temp	HR	BP	RR	SpO2
98.9	46	125/51	18	N/A

The patient appears to be uncomfortable on examination. The abdomen is soft and non-tender without peritonitis. The GU exam is remarkable for developmentally appropriate external male genitalia with no penile discharge. There is significant left testicular tenderness to palpation with some mild edema. No masses are appreciated. The cremasteric reflex is present on the right but absent on the left.

Diagnostic Work-Up

Scrotal ultrasound: On duplex doppler imaging no arterial or venous flow is present in the left testicle compatible with acute left testicular torsion

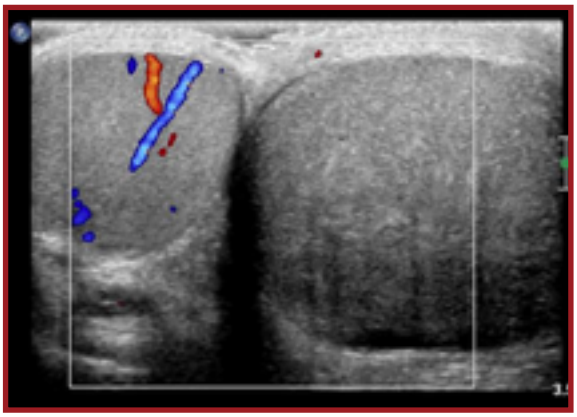

Image 1: Scrotal ultrasound depicting lack of arterial or venous flow in testicle, consistent with testicular torsion

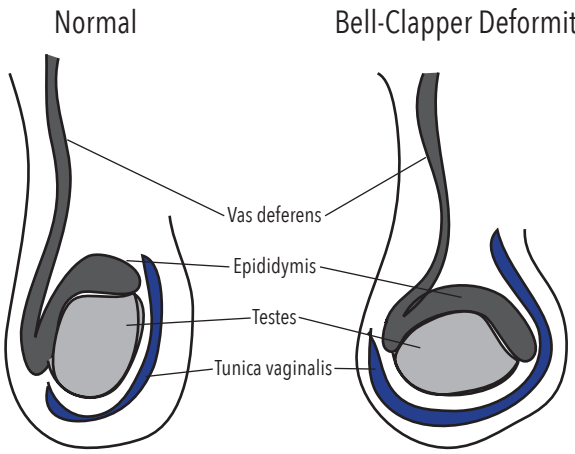

Figure 1: Image depicting bell-clapper deformity (failure of the posterior anchoring of the gubernaculum, epididymis and testis) that can lead to testicular torsion

Hospital Course

The patient was given intravenous morphine and ondansetron for symptomatic relief while in the ED. Urology was consulted and a formal testicular ultrasound was performed which revealed no arterial or venous flow in the left testicle consistent with testicular torsion. The patient was emergently taken to the operating room where he underwent scrotal exploration with detorsion of the left testicle with bilateral orchiopexies. His left testicle was deemed viable in the OR and thus orchiectomy was not pursued. The patient recovered well postoperatively and was discharged home that same day.

Discussion

Testicular torsion occurs in younger males in a bimodal distribution, occurring first in the neonatal period and then again around puberty. This painful phenomenon affects 3.8 per 100,000 males younger than 18 years old each year and accounts for 10-15% of acute scrotal complaints in children.[1] Family history of torsion is the second most common risk factor, after age, for developing testicular torsion.[3] Interestingly, a case series of testicular torsion published in the British Journal of Urology found that testicular torsion was more common during the colder part of the year, specifically when the external temperature was less than 41 degrees farenheit.[4] Anatomic variations can also place patients at higher risk for developing torsion. Occasionally the tunica vaginalis will completely encircle the epididymis rather than attaching to the scrotal wall. This changes the testicular lie from a vertical to horizontal position and allows for more free movement of the testicle. In these patients, the testicle is free to swing like a bell clapper (the moving metal piece inside of a bell) and therefore was appropriately named the bell-clapper deformity. Patients with this deformity are at a higher risk of torsion.[5] Lastly, testicular torsion may occur after direct groin trauma and is often missed with the assumption that the scrotal pain is secondary only to trauma. Due to this, the salvage rate is only around 40% in patients with trauma-induced torsion due to delayed diagnosis.[6]

Testicular torsion occurs in one of three ways. The first is an extravaginal type of torsion that typically affects newborns and involves the twisting of the vas deferens, testicular blood vessels, process vaginalis, and surrounding fascia. The second and most common type of torsion is intravaginal where the testis twists without involvement of the surrounding tunica vaginalis. This type of testicular torsion is how the aforementioned bell-clapper deformity leads to torsion. This second type of torsion typically occurs around the time of puberty.[2] Lastly, there is a third rare form of testicular torsion where the mesorchium—the tissue that overlies the vasculature between the epididymis and parietal tunica vaginalis—undergoes torsion without the testicle itself twisting.[5] Any of the torsions mentioned above lead to blockage of venous outflow which causes vascular engorgement and eventual obstruction of arterial flow, leading to ischemia.[5] More malrotation leads to faster ischemia and infarction, and therefore lower rates of salvage if not diagnosed quickly.[1]

Patients with testicular torsion typically present with sudden onset of severe unilateral scrotal pain with associated nausea and vomiting.[1,7] Occasionally, torsion can present with non-specific symptoms including urinary problems and fever.[1] Only about 10% of patients with testicular torsion will report recent trauma to the area, and some patients will report strenuous physical activity before the onset of symptoms.[1,7]

Physical examination is often remarkable for ipsilateral scrotal tenderness, induration, erythema and warmth which are progressive over time. The absence of a cremasteric reflex is the most common finding, occurring in almost all patients older than 30 months.[8] However, one smaller study demonstrated the presence of a cremasteric reflex in 31% of patients with testicular torsion, limiting its diagnostic utility.[9] Neonatal presentation is often painless and the affected testis may not be erythematous, warm, or edematous.[16] Neonates often lack a cremasteric reflex entirely. An additional helpful sign in the younger patient population is an elevated testicular position.[6,10]

Testicular torsion is primarily a clinical diagnosis, and delayed diagnosis can lead to poor patient outcomes.[1] Emergent urological consultation for surgical exploration is warranted for any patient for whom the emergency provider has a high index of suspicion for testicular torsion, and further imaging should not delay intervention.[4] Ultrasonography is the test of choice when the diagnosis is not entirely clear. As little as 180 degrees of torsion will obstruct venous flow. Any twisting greater than 180 degrees may block arterial flow.[12] Sonographic evidence of decreased venous or arterial blood flow is consistent with the diagnosis of testicular torsion and should prompt emergent urological evaluation.[1] Scrotal ultrasonography has a sensitivity of 88-100% and a specificity of about 90%.[11] Unfortunately, ultrasonographic evaluation may be artificially reassuring in very early presentations as it may fail to adequately demonstrate vascular obstruction.[12]

The definitive treatment of a non-infarcted testicle is surgical detorsion and orchiopexy, ideally within four to eight hours after onset of symptoms. Nonsalvageable ischemic injuries necessitate surgical orchiectomy.[13] If access to urological resources is limited or not readily available, manual detorsion should be attempted in the ED.[1] This can be a very uncomfortable procedure and appropriate analgesia and/or sedation should be administered before any attempts are made. Manual detorsion is performed by rotating the affected testicle away from the midline as if one were opening a book. Some torsions may require up to 720

Testicular torsion
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Methemoglobinemia

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History of Present Illness

The patient was a male in his 50s with a past medical history of recently diagnosed acquired immunodeficiency syndrome (AIDS) with a CD4 count of 16 cells/mm3 who presented to the emergency department (ED) with shortness of breath for one day. He was hospitalized with pneumocystis jerovici pneumonia (PJP) several weeks ago, and was started on combined antiretroviral therapy and azithromycin at discharge. He completed outpatient PJP treatment with oral steroids, primaquine, and clindamycin yesterday. On the day of presentation to the ED, he was profoundly hypoxic on emergency medical service (EMS) arrival at his home, but his oxygen saturation improved to the mid-80s on supplemental O2 via non-rebreather.

Past Medical History

AIDS, syphilis, candida esophagitis, HTN, chronic rash

Past Surgical History

None

Medications

Albuterol, azithromycin, bictegravir/emtricitabine/tenofovir alafenamide, diphenhydramine, MVI, ondansentron

Allergies

Amlodipine, codeine, hydrochlorothiazide, lisinopril, sulfa drugs

Physical Exam

Temp	HR	BP	RR	SpO2
98.4	129	151/69	45	84% NRB

The patient was chronically ill-appearing and in acute respiratory distress. He was markedly tachypneic with increased work of breathing and accessory muscle use. On auscultation, he had diffuse rhonchi bilaterally with poor air entry. He was tachycardic with strong distal pulses and no peripheral edema. He had a diffuse lenticular rash over his chest, back, and upper extremities with no open wounds or sores. His abdominal exam was benign. He was alert and oriented with a normal neurologic exam.

Diagnostic Work-Up

4.0	10.7	215	32.8

137	101	74	129
5.5	20	2.45	

VBG: pH7.33 pCO2 44 pO2 15 HCO3 23 Methgb 20.7%
Lactate 4.3
Ca 9.8 Trop 0.07 BNP 54 D-dimer>20.00 INR 1.2
Urine: +ketones, +glucose, otherwise normal

EKG: Normal sinus rhythm at 63 bpm, normal axis, normal intervals: PR 140 ms, QRS 62 ms, QTC 433 ms.

Hospital Course

The patient was alert on ED arrival, and was initially trialed on non-invasive positive pressure ventilation (NIPPV) without improvement. He remained persistently hypoxic and his mental status progressively declined. He was intubated but remained hypoxic despite escalation of ventilator support. He was noted to have methemoglobinemia on admission that resolved following treatment with methylene blue. Primaquine was the suspected inciting agent, and he was started on atovaquone for PJP treatment. He was covered empirically with broad-spectrum antibiotics and admitted to the medical intensive care unit (MICU).

His chest x-ray showed bilateral pulmonary infiltrates concerning for acute respiratory distress syndrome (ARDS), thought likely to be secondary to PJP or immune reconstitution inflammatory syndrome (IRIS). He remained difficult to oxygenate and ventilate, requiring chemical paralysis for ventilator dyssynchrony, and ultimately developed bilateral pneumothoraces and pneumomediastinum. He required intermittent vasopressor support for septic shock, was continued on antibiotics, and was started on stress-dose steroids. His hospital course was further complicated by acute renal failure with a brief continuous renal replacement therapy (CRRT) requirement, and recurrent episodes of supraventricular tachycardia (SVT). He remained in the MICU for three weeks, during which time he clinically improved but remained ventilator-dependent. A tracheostomy was performed and he was discharged to a long term acute care (LTAC) facility for ventilator weaning and rehabilitation.

Discussion

This was a critically-ill patient whose illness was complex and multifactorial. The ensuing discussion will focus on one particular aspect of his presentation: acquired methemoglobinemia.

Pathophysiology

Methemoglobin (metHb) formation occurs when the iron moiety in hemoglobin is oxidized from the ferrous (Fe2+) to ferric (Fe3+) state. This triggers an allosteric change in the hemoglobin molecule, increasing affinity for oxygen at the remaining heme sites in the hemoglobin tetramer, while the metHb unit itself is unable to bind or carry oxygen. Oxidative stress causes baseline conversion of hemoglobin to metHb at a rate of about 3% per day.[1] In healthy individuals, however, physiologic counter-regulation maintains the overall level of metHb at less than 1%. The primary enzymatic pathway by which this occurs is the cytochrome b5-metHb reductase pathway, in which NADH acts as a cofactor for reduction of metHb to hemoglobin. An alternative pathway via NADPH-metHb-reductase is minimally functional under physiologic conditions, but can be activated by an exogenous electron acceptor such as methylene blue. Clinically-significant methemoglobinemia can develop when metHb production exceeds the physiologic capacity for reduction and causes hypoxia. Tissue hypoxia occurs via two mechanisms: a leftward shift in the oxygen-hemoglobin dissociation curve and a functional anemia due to decreased oxygen bind-

ing capacity.[1,2,3]

Methemoglobinemia is further dichotomized into either a hereditary or acquired disease. Hereditary methemoglobinemia is caused by decreased or dysfunctional enzyme activity or the presence of an abnormal hemoglobin that cannot be reduced.[1] Acquired methemoglobinemia results from increased metHb production, most commonly due to ingestion or topical exposure to an exogenous medication or chemical. These agents cause direct oxidation of hemoglobin to methemoglobin or indirect oxidation through reduction of oxygen to a free radical that in turn oxidizes hemoglobin.[4] Many medications are not oxidizing agents themselves, but are instead metabolized to oxidative free radicals. Individual variation in metabolism may explain why some patients develop methemoglobinemia with exposure to a given medication while others do not.[4]

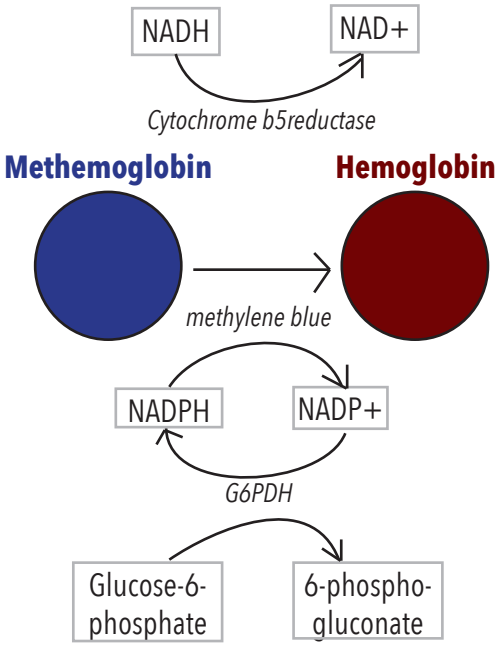

Figure 2: Reduction cycle of methemoglobin to hemoglobin

Environmental or occupational toxins implicated in methemoglobinemia include compounds found in dyes, pesticides, herbicides, and explosives. The most common toxins include nitrates, nitrites, chlorates, and aniline derivatives.[1,4]

Most cases of methemoglobinemia result from medication exposures, and the list of potentially-causative agents is extensive (see Table 1). One retrospective review identified dapsone as the most common inciting agent (42% of cases), followed by benzocaine and primaquine (4% each).[5] Acute or chronic illness may also contribute to oxidative stress, and clinically-significant methemoglobinemia is often the result of an exogenous exposure superimposed on other underlying stressors or comorbidities.[6]

While acquired methemoglobinemia is more common in adults and older children, it may occur in young infants via several unique mechanisms. It has been described in infants fed pureed vegetables with high nitrate content (e.g., beets, spinach) as well as formula reconstituted with nitrate-contaminated well water.[7,8] Methemoglobinemia due to transcutaneous absorption of aniline dye used to mark fabric has also been reported in infants, though this is of more historical interest than practical concern.[9] Today, infantile methemoglobinemia most often occurs idiopathically in the setting of metabolic acidosis due to dehydration, diarrheal illness, or sepsis, or as a result of exposure to oxidative medications, including topical anesthetics used to treat teething pain.[3,4,5,6,10]

Clinical Presentation

The symptoms of methemoglobinemia generally correlate with metHb level, though they may be exaggerated in patients with concurrent anemia, respiratory illness, or cardiovascular disease.[1] Cyanosis typically becomes apparent at levels between 10 - 20% of total hemoglobin, and is often out of proportion to oxygen saturation as measured by pulse oximetry. As metHb levels increase, patients may become tachycardic, tachypneic, anxious, confused, and complain of headache or fatigue. Significant neurologic and cardiovascular symptoms develop at levels greater than 50%, including seizure, coma, and arrhythmias. MetHb levels greater 70% are typically fatal.[4]

While the symptoms of methemoglobinemia are largely non-specific, certain contextual findings should prompt its consideration in a patient with refractory hypoxia and cyanosis. A thorough medication review is of the utmost importance as this can aid physicians in making the diagnosis. Though this may be difficult to diagnose, methemoglobinemia should be considered in patients who have AIDS or are otherwise immunocompromised, as they may be taking dapsone, primaquine, or Bactrim for PJP prophylaxis. Methemoglobinemia can also present with patients who have undergone a recent procedure employing topical anesthesia, such as transesophageal echocardiography, bronchoscopy, or EGD. Patients who have been prescribed topical agents for sore throat, such as benzocaine-containing "HurriCaine" spray can also develop clinically significant methemoglobinemia. Finally, metHb levels should be checked in patients who present following an industrial accident with hypoxia or cyanosis.

Diagnostic Evaluation

Blood containing high levels of MetHb is classically described as chocolate brown in color and will not turn red when exposed to oxygen. An oft-described bedside test involves placing a drop of blood on a piece of filter paper and observing for color change, which can be accelerated by blowing supplemental O2 on the paper. Blood that remains brown suggests an elevated metHb level.[1,5,11] The presence of a "saturation gap" between peripheral oxygen saturation and measured arterial oxygen content by blood gas analysis should also raise suspicion for methemoglobinemia. In standard pulse oximetry, oxygen saturation is calculated from the ratio of light absorbance at two specific wave-

Patient population	Threshold Methgb level for treatment
Healthy, asymptomatic adults	>30%
Infants	>20%
Adults with co-morbidities, poor physiologic reserve	>10%
Symptomatic adults OR patients with evidence of tissue hypoxia (metabolic acidosis)	At any level

Table 1: Threshold levels for treating methemoglobinemia in certain patient populations

Methemoglobinemia
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LONG QT SYNDROME

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History of Present Illness

A two-year-old male with a history of congenital long QT syndrome (LQTS) involving mutation of the LQT2 gene on daily propranolol presented after reportedly having an episode of unresponsiveness at home. The patient's mother stated that the patient was previously in his usual state of health and received his dose of propranolol the prior night. Upon awakening that morning, the patient was sweaty, cold to the touch, and irritable. He then started to stare off into space, subsequently becoming unresponsive with sudden loss of tone and tonic-clonic movements.

Upon EMS arrival, the patient had a blood glucose in the 30s and was treated with intramuscular glucagon and parenteral dextrose. Subsequent repeated finger stick blood glucose remained in the 30s and Air Care was called to the scene.

Past Medical History
Long QT Syndrome

Medications
Propanolol

Past Surgical History
Bilateral myringotomy

Allergies
None

Physical Exam

Temp	HR	BP	RR	SpO2
34.9	50	85/64	31	99% RA

Age appropriate two-year-old male who is obtunded and not responsive. His lungs were clear bilaterally and his heart had a regular rate and rhythm. His abdomen was soft and non-distended. His extremities were cool to the touch with delayed capillary refill. Bruising and edema was present on RLE at the site of the attempted IO placement. His pupils were equal and reactive, he did not respond to voice or follow commands, and did not localize to central painful stimuli or withdraw from peripheral painful stimuli.

Diagnostic Work-Up

VBG: pH7.22 pCO2 59.4 HCO3 27 BE-4
Ca 9.1 Phos 5.0 Alb 4.1
Urine: +ketones, +glucose, otherwise normal

EKG: Normal sinus rhythm at 63 bpm, normal axis, normal intervals: PR 140 ms, QRS 62 ms, QTC 433 ms.

Hospital Course

Upon Air Care arrival, the patient was bradycardic in the 50s with otherwise normal vital signs, and unresponsive. The medical crew administered a second dose of parenteral glucose and the patient became more responsive but still drowsy and confused. A repeat finger stick glucose was 349. He received a dose of Zofran and was warmed with blankets. He remained stable throughout the flight and was transported to a tertiary childrens hospital in stable condition.

In the emergency department (ED), the patient was initially hypothermic and warmed with a Bair Hugger, blankets, and warmed IV fluid bolus. He intermittently had bradycardia to the 50s, which improved with stimulation. The patient had blood cultures drawn and was started on Ceftriaxone for empiric sepsis coverage. The patient's respiratory acidosis was thought to be due to hypoventilation from a post-ictal period after a presumed seizure. Beta-blocker overdose remained high on the differential, although the patient's parents were adamant that the patient did not receive any more than his usual dose. The patient was admitted to the pediatric intensive care unit (PICU) for continuous monitoring and further workup.

The patient was evaluated by cardiology and endocrinology during his hospitalization. His EKG in the emergency department revealed a rate of 63 and a normal QTc of 433ms, both of which were likely due to continuation of his propranolol. He had no QTc prolongation, arrhythmias, or seizure-like episodes. His heart rate remained in the 70s-110s during his hospitalization and he was continued on his home dose of propranolol. He is undergoing a 30-day outpatient event monitor currently.

The etiology of his hypoglycemia was not definitively identified during his initial hospitalization but thought to be secondary to ketotic hypoglycemia versus decreased oral intake in setting of viral illness worsened by blunting of his body's natural response to hypoglycemia by propranolol. There are also reports of congenital LQTS mutations being associated with abnormal glycemic regula-

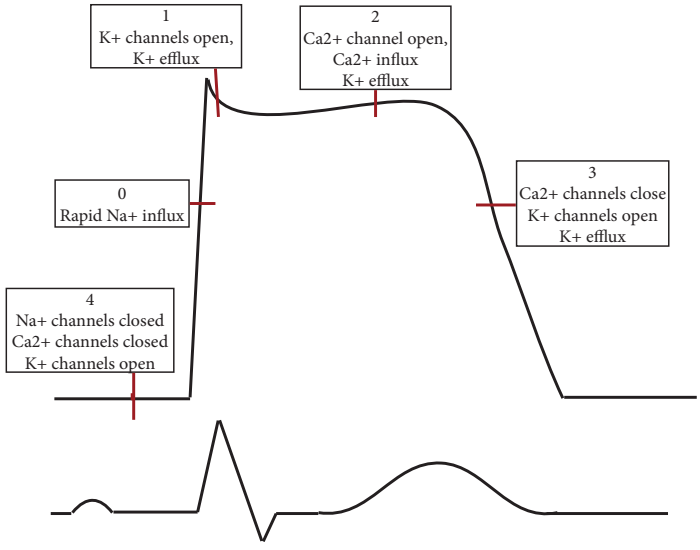

Figure 3: Graph depicting the cardiac action potential in association with QT interval

tion. He was subsequently admitted for a hypoglycemia challenge and diagnosed with ketotic hypoglycemia. His seizure was thought to be secondary to his hypoglycemia.

Discussion

While this patient's hospitalization primarily focused on diagnsosis and treatment of his hypoglycemia, the discussion to follow will focus on the pathophysiology and management of LQTS and the malignant arrhythmias that may develop in these patients.

QT Upper Limit of Normal	
Prepubertal children	460ms
Adult males	470ms
Adult females	480ms

Table 2: Upper limit of QT interval values

LQTS is an EKG abnormality which can be congenital or acquired, and is characterized by lengthening of the QT interval as measured from the start of the QRS complex to the termination of the T-wave, which represents the depolarization-repolarization cycle of the ventricles. LQTS is generally a disorder of repolarization rather than depolarization. Depolarization occurs through the influx of sodium and calcium, and repolarization occurs through the outflow of potassium through channels in the myocardial membrane.[1] (Figure 1) When corrected for heart rate (called the QTc interval), the upper limit of normal for prepubertal children is 460ms, 470ms in adult males, and 480ms in adult females.[2] Lengthening of the QTc beyond these durations can lead to Torsades de Pointes (figure 2) or ventricular fibrillation, which can subsequently lead to syncope or even sudden cardiac death. A meta-analysis performed by Zhang et al found that QT-interval length is a determinant of mortality in the general population.[3]

Congenital LQTS is estimated to have a prevalence of approximately 1:2000.[5] Mutations in ten genes have been linked to congenital long QT. However, the best described mutations are LQT1 and LQT2, which are mutations in potassium channels, and LQT3 which is a mutation in a sodium channel. Together these mutations comprise over 75% of the cases of congenital LQTS. The penetrance of these mutations is highly variable and some patients will have normal QTc intervals and remain completely asymptomatic throughout life even when they test positive for the mutations. Sudden cardiac death, however, was the initial manifestation in 13% of cases in a retrospective review.[13]

Medications Associated with LQTS	
Antibiotics - Fluoroquinolones - Macrolides - Trimethoprim - Pentamidine - Azole antifungals	**Antiarrhythmics** Class IA: Na+ channel blockers - *Quinidine** - Procainamide - Disopyramide Class III: K+ channel blockers - *Amiodarone** - *Sotalol** - Dofetilidev - Ibutilide - Dronedarone
Antipsychotics - Haloperidol - Droperidol - *Thioridazine** - Pimozide	
Antiemetics - Ondansetron - Granisetron - Metoclopramide	**Poses the greatest risk of QT prolongation in this category*

Table 3: Medications associated with prolonged QT syndrome

Causes of acquired LQTS include hypokalemia, hypocalcemia, hypomagnesemia, and drugs. Many drugs (table 1) have been implicated in lengthening of the QT interval, but class IA and III antiarrhythmics and psychotropic medications are the most common medications that prolong the QT interval.[6] Electrolyte abnormalities or drugs that prolong the QT interval can unmask LQTS in patients with a genetic predisposition who otherwise may have been asymptomatic.

Typically, patients who present to the emergency department that are symptomatic from LQTS will have a history of palpitations, syncope, presyncope, seizures, or cardiac arrest.[4] Classic triggers for symptoms include exercise, emotional stress, diving or swimming, and loud noises.[4] Patients who are seen in the emergency department reporting syncope or seizure activity should have an EKG to screen for LQTS. While the EKG machine calculates the QTc, the QT interval needs to be closely inspected and manually calculated if it appears prolonged. Leads II and V5 are conventionally used to measure the QTc. If a U wave is present, this should not be included when measuring the QT interval. A QTc greater than 480ms in pediatric patients or 500ms in adults on a screening EKG needs to be further evalutated. Any culprit drugs should be discontinued and metabolic abnormalities must be corrected aggressively. Risk factors for LQTS should be carefully assessed prior to administering a QT-prolonging medications in the emergency department (Table 2).[1] If a patient presents with unstable Torsades de Pointes, the treatment is defibrillation; if stable, they should receive intravenous magnesium sulfate and overdrive transvenous pacing if persistent.[6,7] Several studies have shown

Risk factors	Implication for QTc prolongation
Age	Increasing age predisposes bradycardia and opportunity for longer repolarization interval
Sex	Females have greater tendency for drug-induced Torsades
Hemodynamic instability and electrolyte abnormalities	Predisposition to reentrant arrhythmia
Cardiac abnormality	Bradycardia prolonging repolarization
Treatment with other QT-prolonging medications	Drug-drug interactions, additive effects
Congenital LQT	Abnormalities in cardiac sodium and potassium channels

Table 4: Risk factors for developing prolonged QT

Long QT Syndrome
continued on page 14

Leprosy

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History of Present Illness

The patient was a middle aged male with a past medical history of leprosy who presented to the emergency department (ED) with malaise, fevers, and a worsening rash. The patient recently emigrated from Micronesia to the United States six months prior to his presentation. The patient was diagnosed with leprosy at 12 years of age and had been taking two unknown medications for the past 15 years. Upon emigration, the patient stopped taking these medications subsequently leading to progressive malaise, fevers, and skin lesions. The patient denied any associated pain, numbness, or altered sensation.

Past Medical History
Leprosy

Past Surgical History
None

Medications
None

Allergies
No known allergies

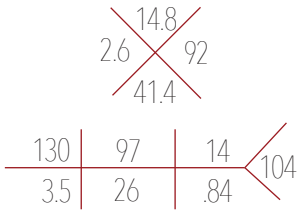
Social History
Endorses use of cigarettes, marijuana and alcohol daily

Physical Exam

Temp	HR	BP	RR	SpO2
98.5	72	102/64	15	95%

The patient appeared uncomfortable. He had no mucosal lesions or conjunctival injection. The patient's neck was supple. His lungs were clear; heart was regular and without murmurs. The patient's feet were swollen bilaterally with strong peripheral pulses in the lower and upper extremities. There were multiple papular lesions in varying stages on the trunk and extremities; some appeared granulomatous and open with scabs while others were raised (pictures below). The lesions were not tender to palpation. His neurological exam was normal.

Diagnostic Work-Up

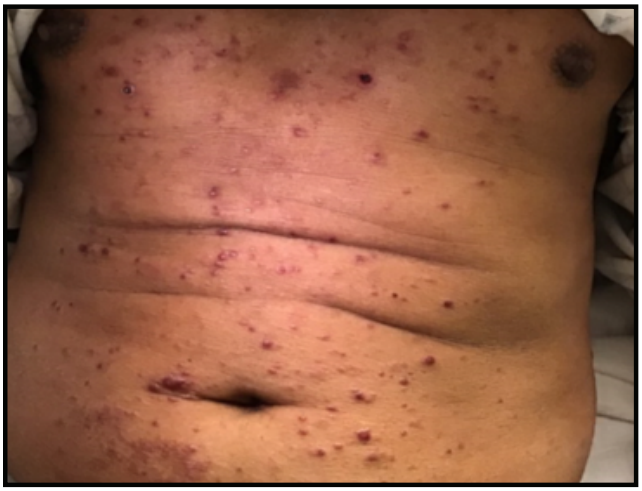


HIV: Non-reactive
RPR: Non-reactive

Imaging
Chest X-ray PA and Lateral:
No acute cardiopulmonary disease.

Hospital Course

While in the emergency department, the providers were concerned for a reactivation of the patient's known leprosy. Dermatology was contacted and recommended admission to the hospital for biopsy, which revealed acid-fast bacilli. Infectious disease was consulted, and the patient was started on Dapsone and Rifampin. Dapsone and Rifampin were subsequently stopped during his hospital stay given concern for antibiotic resistance, and the patient was started on Minocycline and Clarithromycin. Ophthalmology evaluated the patient and did not appreciate any ocular manifestations of leprosy. He was treated with intravenous steroids as an inpatient and was transitioned to a prolonged oral steroid taper to be completed in the outpatient setting. This was eventually bridged to methotrexate. The patient's thrombocytopenia and leukopenia remained stable while inpatient and were attributed to alcohol use and immunosuppression from a recent viral illness. He has been followed as an outpatient and continues his multi-drug regimen for lepromatous leprosy.



Images 2-4: Image depicting patient's skin findings consistent with leprosy.

Discussion

Leprosy is a chronic infection caused by an acid-fast bacterium named Mycobacterium leprae (M. leprae).[1] It is a highly contagious disease that affects the skin and peripheral nerves, and the first known cases date back to over 3000 years ago.[1] Currently, morbidity is generally low as much of the population has a natural resistance to the disease.[1]

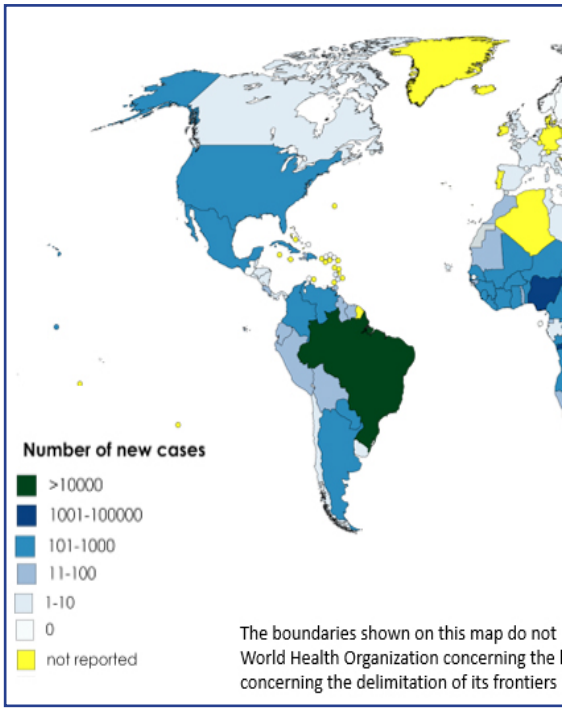
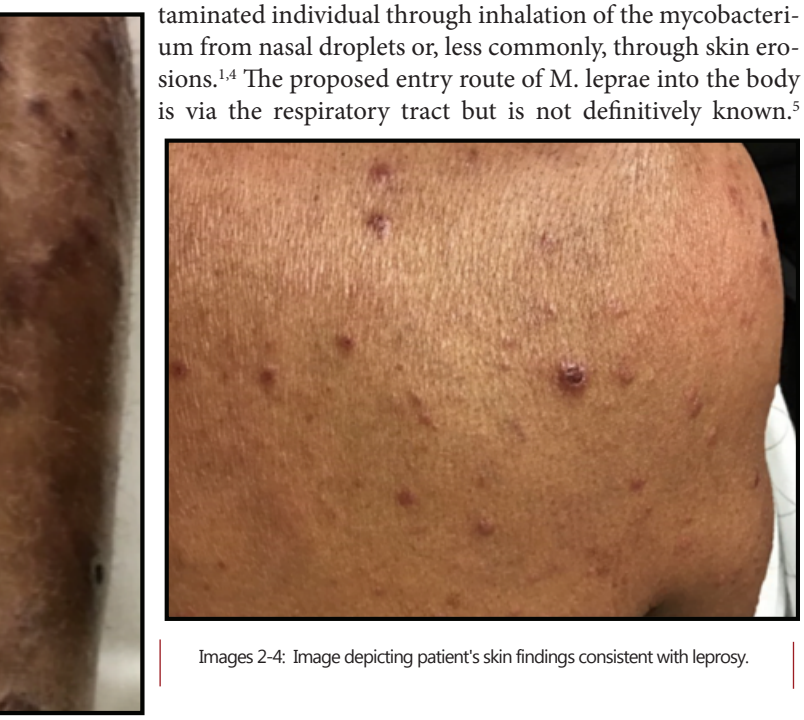


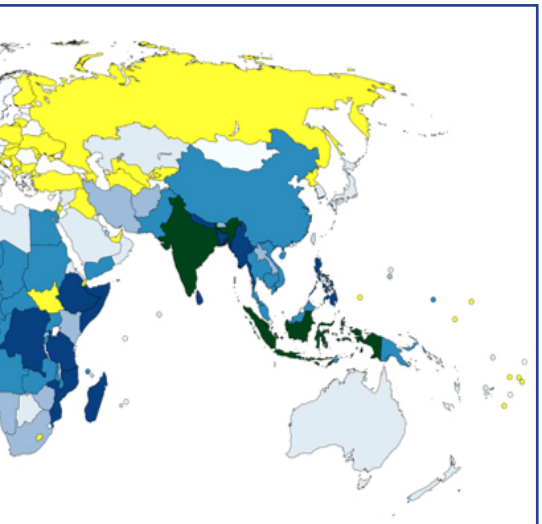
Figure 4: Image depicting geographical distribution of new leprosy cases, *who.int/entity/global_leprosy_programme/epidemiology/en/*

The incidence of leprosy has been slowly decreasing over the past 15 years.[2] Seventy-five percent of new cases occur in South-East Asia, with India accounting for sixty percent of new cases in 2015.[2,3] Other endemic areas include South America, Africa, Western Pacific, and Eastern Mediterranean countries.[2] One study showed that humans and armadillos in the southwestern United States carry similar strains of leprosy, suggesting a zoonotic connection.[3]

Transmission is from prolonged close-quarter contact with a contaminated individual through inhalation of the mycobacterium from nasal droplets or, less commonly, through skin erosions.[1,4] The proposed entry route of M. leprae into the body is via the respiratory tract but is not definitively known.[5]



Images 2-4: Image depicting patient's skin findings consistent with leprosy.



imply the expression of any opinion whatsoever on the part of the egal status of any country, territory or area or its authorities, or or boundaries.

2016. *Image courtesy of World Health Organization: http://www.searo.*

M. leprae is then consumed by macrophages, skin cells, and Schwann cells where it proliferates, leading to cellular damage.[1] The severity of disease is related directly to the immune response driven by the body.[5] Leprosy can present as a single skin lesion or multiple lesions.[5] People can remain asymptomatic for several years and may even clear the bacteria before manifesting any clinical signs of the disease.[4] There have been several genes that are related to an increased susceptibility to leprosy and put the patient at a pre-disposition to the various leprosy subtypes discussed below.[1]

Tuberculoid leprosy is the most benign subtype of leprosy. Tuberculoid leprosy presents as larger hypo-pigmented nodular skin lesions with granulomatous changes, absent hair, and sensation loss. Patients with the tuberculoid subtype of leprosy have a robust immune response consisting of CD4+ cells and Th1 cells resulting in granuloma formation.5

Lepromatous leprosy presents with innumerable small maculular or papular lesions over the whole body with hair growth and no sensory loss. Lepromatous leprosy is related to a predominate CD8+ and Th2 response.[5]

Finally, many patients present with a mix of these subtypes. They often present a variety of both clinical findings that fall somewhere between the tuberculoid and lepromatous leprosy subtypes.[5]

Chronic leprosy can lead to multiple reactional states of acute inflammation.[5] The first reactional state is a Type I reaction, also known as reversal reaction, resulting from an intensified T cell response which leads to increased inflammation of the leprosy lesions and worsening neuritis. Type I reactions are associated with initiation of therapy and are treated with steroids. Type II reactions, also known as erythema nodosum leprosum, are related to a humoral response associated with the development of painful subcutaneous lesions, fever, and malaise.[6,7,8] It results in immune complex depositions and diffuse vasculitis. Type II reactions are more commonly seen in the lepromatous leprosy subtype, and they are treated with thalidomide.

Diagnosis

According to the World Health Organization, the diagnosis of leprosy can be clinical and is based on the presence of lesions consistent with leprosy and coexistant sensory loss. Unfortunately, many patients experience a significant delay in diagnosis because of the rarity of this disease in the United States. Therefore, providers should be keenly aware of the characteristic skin lesions, and concomitant sensory involvement should increase suspicion for this diagnosis. A thorough travel history should also be taken in any patient presenting with concerning symptoms.

Skin smears positive for acid fast bacilli can confirm the diagnosis, although this is often delayed and is highly dependent on the bacterial load of a lesion. Biopsy and acid fast staining of an affected area is helpful in a lesion with a high bacterial load. In patients with low bacterial loads, biopsy and stain is often not enough for definitive diagnosis. Polymerase chain reaction, serology, and histopathology can further assist with this diagnosis.[9]

Treatment

Patients presenting to the emergency department with symptoms suggestive of leprosy warrant emergent dermotologic consultation. As leprosy is transmitted via nasal droplets and prolonged close contacts, these patients should be placed in droplet precautions in the ED. These precautions should be continued for 72 hours after the initiation of therapy. Admission may be necesssary until the diagnosis can be confirmed and appropriate treatment initiated. Many patients will experience reactions after treatment initation, so a period of inpatient observation may be helpful to guide management.

Leprosy
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CALCIUM CHANNEL BLOCKER TOXICITY

Kelly Brookbank, Pharm D
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Beta blocker (BB) and calcium channel blocker (CCB) overdose is associated with a high incidence of morbidity and mortality from cardiovascular toxicity, including profound hypotension and conduction disturbances.[1,2] Mortality and morbidity cannot be predicted from dose alone, and therefore all BB and CCB overdoses should be managed promptly and aggressively.[3,4]

Pathophysiology

Beta-1- adrenergic receptors activate adenyl cyclase to increase cyclic AMP (cAMP) production and thereby increase phosphorylation and the opening of L-type calcium channels.[2] BBs antagonize the beta-1 adrenergic receptors, which reduces calcium entry into cardiomyocytes and results in negative chronotropic and inotropic effects.[2] CCBs directly inhibit voltage-gated L-type calcium channels from opening, preventing calcium influx into the myocardial and vascular smooth muscle cells.[2] Calcium influx is vital to the electrical conduction within the myocardium as well as the maintenance of vascular and gastrointestinal smooth muscle tone.[2] CCBs also inhibit L-type calcium channels in the pancreatic islet cells, reducing insulin secretion.[2] In a CCB overdose, hyperglycemia and reduced cardiac glucose utilization maybe observed.[1,2] In both BB and CCB overdoses, decreased calcium entry will lead to impaired conduction and muscle contraction, ultimately resulting in hypotension, bradycardia, decreased systemic vascular resistance, and cardiogenic shock.[1,2]

Beta Blocker Solubility and Duration

Beta Blocker	Lipid solubility	Time to peak effect	Half-life
Atenolol	Low	2-4 hrs	6-7 hrs ESRD: 15-35 hrs
Bisoprolol	Moderate	1-2 hrs	9-12 hrs CrCl <40ml/min: 27-36 hrs Cirrhosis: 8-22 hrs
Carvedilol	Moderate	IR: 1-2hrs ER: ~5 hrs	7-10 hrs
Labetalol	Moderate	PO: 2-4 hrs IV 5-15 min	PO: 6-8 hrs IV: 5.5 hrs
Metoprolol	Moderate	PO: 1-2 hrs IV: 20 min	3-4 hrs
Nadolol	Low	3-4 hrs	20-24 hrs Severe renal impairment: up to 45 hrs
Propanolol	High	1-2 hrs	IR: 3-6 hrs ER: 8-10 hrs

Table 5: Beta Blocker Solubility and Duration

Early Management

It is vital to determine the formulation of the medication ingested (immediate or delayed release), as this will influence onset and duration of symptoms.[2] Initial management of CCB and BB overdose is primarily supportive care based on cardiac function and hemodynamic status.[1,2,4,5] If an asymptomatic patient presents after ingesting a potentially toxic amount of CCB or BB, it is reasonable to consider pharmacologic treatment of CCB/BB overdose. This includes early gastrointestinal decontamination with activated charcoal.[4] Although there are various recommendations, the most recent toxicology guidelines recommend activated charcoal if a patient presents within two hours of ingestion.[2,4,5] It is also important to consider the pharmacokinetics of the various types of BB/CCB, especially their lipid solubility. Medications with a higher lipid solubility will lead to more profound neurologic symptoms and have a prolonged effect. If a patient has ingested a highly lipid soluble medication and presents within 2 hours of ingestion, activated charcoal should be strongly considered to prevent absorption. Of note, activated charcoal has a substantial aspiration risk of 4-25% which should be considered prior to administration.[9,10]

First-line Therapy

In addition to supportive care, potential interventions include calcium, hyperinsulinemia euglycemia (high dose insulin), inotropes, vasopressors, and atropine. IV calcium is a recommended first line therapy in CCB overdose due to its ability to improve cardiac conduction and blood pressure.[4,6] Calcium is used to reverse the hemodynamic effects of BBs and CBBs by overcoming inhibited calcium channels and increasing inotropy.[1] Although calcium is recommended as a first line therapy, its therapeutic effect is not consistent and it may not be effective in life-threatening overdoses. It is typically given in concert with other recommended therapies.[1,2]

Current literature supports the utility of hyperinsulinemia euglycemia insulin therapy (HEIT) in the treatment of both BB and CCB overdose.[1,2,4,7,8] High dose insulin (1-10 units/kg/hr) promotes inotropy by activating calcium and potassium channels to generate ATP and promoting aerobic metabolism.[7] Observational studies, case series, and animal studies demonstrate an improvement in contractility, blood pressure and a potential increase in survival

with the use of high dose insulin.[4] Animal studies demonstrated a decrease in mortality with high dose insulin therapy compared to those treated with epinephrine or glucagon.[7] High dose insulin stimulated more efficient myocardial carbohydrate metabolism compared to glucagon and epinephrine.[7] In 12 of 13 human case reports, high dose insulin therapy temporarily improved refractory hypotension and reduced vasopressor requirements.[7] Therefore, high dose insulin therapy can reduce the dose of catecholamine infusions and related side effects.[2] High dose insulin therapy can cause hypoglycemia and hypokalemia.[2] Therefore, potassium and blood glucose need to checked prior to initiation and must be closely monitored and aggressively treated.[2] Insulin is titrated to desired heart rate and systolic blood pressure, up to a maximum of 10 units/kg/hr. Blood glucose levels need to be closely monitored to prevent hypoglycemia given the large doses required with HEIT. Dextrose infusions (D10%, D20%, or D70%) should be used in concert with HEIT and titrated to goal blood glucose concentrations of 150-250mg/dL.[1,2,5,7]

Norepinephrine and/or epinephrine are indicated in the presence of shock.[4] In CCB and BB overdoses, response to catecholamines can be unpredictable and very high doses may be required due to the degree of beta-1 antagonism.[2] No single catecholamine has been shown to be superior compared to others in CCB or BB overdose.[2] Norepinephrine is recommended to increase blood pressure and epinephrine is recommended to increase inotropy and chronotropy.[4]

Atropine is indicated for the treatment of symptomatic bradycardia.[1,2] Atropine may treat bradycardia initially, but may not be beneficial in severe toxicity as it is quickly metabolized.[1,2] Atropine can be given as 0.5-1mg IV push every 2-3 minutes with a maximum of 3mg.

First Line Therapy
• IV Calcium Chloride 10% 2gm IV push, followed by 2g/hr IV infusion • Hyperinsulinemia euglycemia insulin therapy (HEIT): insulin infusion 1 unit/kg IV bolus, followed by 1-10unit/kg/hr with Dextrose 10%, 20%, or 70% titrated to maintain blood glucose of 150-250mg/dL • Norepinephrine and/or epinephrine in the presence of shock • Atropine 0.5-1mg (max 3mg) IV every 2-3 min for bradycardia
Refractory to First Line Therapy
• Lipid emulsion Therapy (20%). Infuse 500mL over 30 minutes • Methylene Blue. 1-2mg/kg IV as a single bolus

Table 6: Key points illustrating first line therapies and those used in refractory cases

Agents if Refractory to First-Line Therapy

If patients remain refractory to first line therapy, lipid emulsion or methylene blue may be considered. Outcomes related to lipid emulsion therapy in CCB and BB overdose are variable.[2] It has been reported to have a positive response when given as a rescue therapy, but has not illustrated an effect on hemodynamics.[2] Methylene blue has shown improvement in hypotension from vasodilatory shock refractory to vasopressors in amlodipine and quetiapine overdoses.[2] Of note, glucagon has been shown to have a positive inotropic, chronotropic, and dromotropic effect in CCB.[1,2] However, animal studies indicate that high dose insulin therapy increased survival compared to high dose epinephrine, glucagon, and calcium therapy.[1] Additionally, glucagon can cause nausea, vomiting, and hypercalcemia.[2]

BB and CCB overdoses are associated with high morbidity and mortality and thus need to be promptly treated. All patients presenting with BB/CCB overdose should be provided with supportive care immediately. If the patient becomes hemodynamically unstable, calcium, fluid resuscitation, HEIT, and vasopressors should be started immediately, and secondary agents can be added as needed.

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Leprosy

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Like other mycobacterium, leprosy has high rates of resistance requiring multi-drug regimens to eradicate the disease. According to the World Health Organization, the first line treatment is dapsone and rifampicin for all patients with leprosy. Clofazimine is added to patients with large bacterial loads with at least five lesions. Treatment can last up to 18 months. Alternative treatments include olfloxacin, minocycline, and clarithromycin. Leprosy reactions should be treated with steroids or other immunosupressants.[9]

The National Hansen's Disease Program is a resource for patients affected by leprosy being treated in the United States or its territories. The National Hansen's Disease Program is located in Louisiana and provides free diagnostic services and antibiotics for individuals affected by leprosy.[10] Ultimately, this

Leprosy *continued on page 15*

Valproate Toxicity

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University of Cincinnati R1

History of Present Illness

The patient is a transgendered female in her 20s with a history of bipolar disorder and borderline personality disorder who was initially brought to an inpatient psychiatric hospital by her probation officer for erratic behavior. While in the facility's intake area, staff observed her ingest between 4,000 and 16,000 mg of liquid valproate, which she had previously been prescribed for her bipolar disorder. The patient was immediately transferred by emergency medical services to the emergency department (ED) for evaluation.

Past Medical History

Bipolar disorder
Borderline personality disorder
Post-traumatic stress disorder
Hypertension

Past Surgical History

Orchiectomy

Social History

The patient lives in a group home. She is a current smoker.

Medications

Valproate syrup
Quetiapine
Estradiol

Allergies

Penicillin

Physical Exam

Temp	HR	BP	RR	SpO2
97	86	128/81	15	98%

The patient is an anxious appearing woman. Cardiovascular exam reveals a normal rate and rhythm. Lungs are clear to auscultation with normal respiratory effort. There is mild tenderness to palpation in the right upper quadrant of the abdomen. The patient is alert and oriented to self, place, time, and situation. Pupils are equal, round, and reactive to light. There is no asterixis. The neurologic examination is otherwise unremarkable and without focal findings.

Diagnostic Work-Up

Valproate 239 µg/mL (ref range 50-100 µg/mL)
Ammonia 127 µg/mL (ref range 27-90 µg/dL)

EKG: normal rate and rhythm, normal axis, and no ST segment changes. The patient's QTc was noted to be 495 ms.

Hospital Course

While the patient's vital signs and mental status were normal at presentation, she was noted to be more lethargic and was slurring her words 30 minutes after initial presentation. The patient then revealed that she had taken an additional "wine-glass" of valproate liquid the previous night. The estimated total amount of valproate ingested between the two incidents was between 9,000 and 33,500 mg. Local poison control was consulted for guidance in the medical management of the patient's ingestion.

At 3 hours after her initial presentation, her valproate level was 236µg/mL, and her ammonia increased to 228 µg/dL. The patient's mental status continued to deteriorate, and ED providers administered three grams of L-carnitine in conjunction with poison control. The patient was admitted to an inpatient medicine service for monitoring of her clinical toxidrome, as well as laboratory ammonia and valproate levels, with a plan to perform dialysis if her mental status worsened. Her L-carnitine dose was repeated every 8 hours. The patient's valproate and ammonia levels steadily decreased over the course of her stay. Her lethargy and altered mental status gradually resolved, and she was discharged to inpatient psychiatry for further evaluation.

Discussion

Principles of Management

Valproate - also known as valproate sodium, valproic acid, VPA, or by the brand names Depakote, Depakene, and Depacon – is a short chain fatty acid used as an anticonvulsant in epilepsy, a mood stabilizer in bipolar disorder, and a prophylactic agent for migraine headaches. Valproate is available in a variety of formulations, including both extended release and immediate release, and may be administered as a tablet, liquid, or intravenously. While its mechanism of action is not completely understood, it is known to have actions potentiating GABA activity, while inhibiting NMDA activity and certain sodium channels.[1]

Patients with acute valproate toxicity may present with depressed mental status, depressed respiratory drive, seizure, or signs of multiorgan dysfunction. Imaging may demonstrate cerebral edema, and laboratory evaluation may demonstrate hepatotoxicity, hyperammonemia, metabolic acidosis, thrombocytopenia, or acute pancreatitis.[2,3] Depressed mental status is the most common clinical sign of valproate toxicity. The level of mental status depression varies with the degree of intoxication, though it is poorly predicted by blood drug levels.[2,4] Severe ingestions have reportedly mimicked brain death.[5] Patients unwilling or unable to provide history will require a broad workup of their altered mental status to rule out other co-ingestion or co-morbidities.[6]

As with any patient, initial actions by the emergency provider include assessment and intervention on immediate threats to airway, breathing, and circulation. Clinical history, with attention to timing, dose, and formulation of the valproate ingestion may help predict the patient's clinical course. Evaluation for co-ingestants or other self-injurious behavior is crucial in known or suspected intentional overdose. Providers should involve a toxicologist or local poison control as soon as possible.

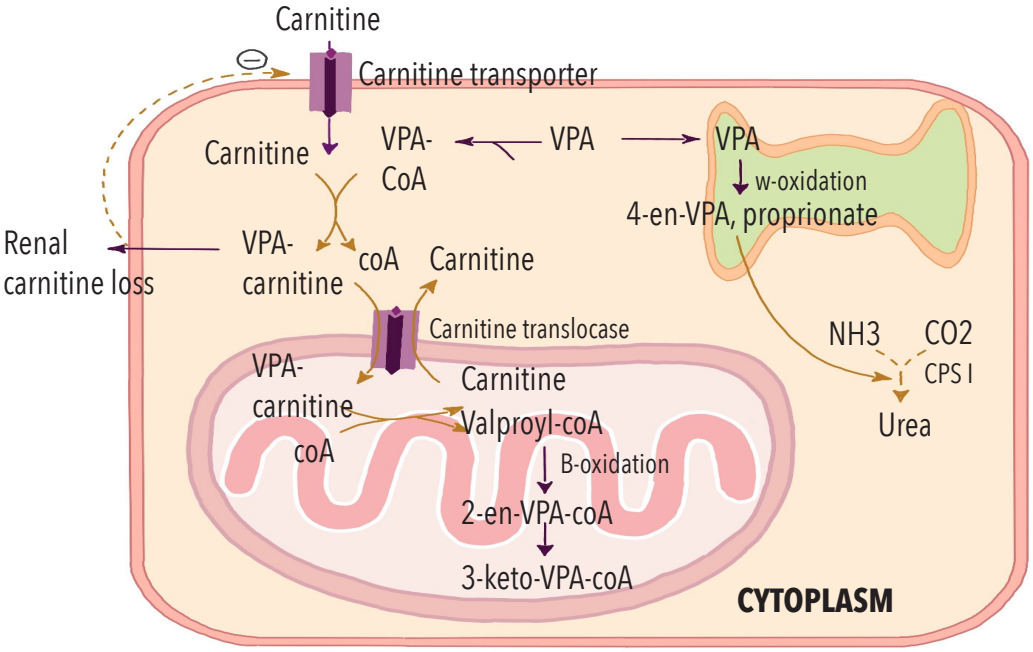

Figure 5: Diagram illustrating oxidative metabolic pathways for valproate.

The timeline of acute valproate toxicity depends on the formulation ingested. With immediate release formulations, peak levels are expected within four hours. With extended or delayed release formulations, peak concentrations may be seen up to 12 hours after ingestion.[7]

Valproate is among the anticonvulsants with rapidly available blood level laboratory tests available in most ED settings. Serial measurements documenting declining valproate levels are used to ensure clearance and appropriate disposition.

Mechanism of Toxicity

Valproate is primarily metabolized by the liver via glucuronidation. Approximately 80% of the breakdown and eventual elimination of the drug occurs via this mechanism under therapeutic circumstances. The remaining 20% of valproate is metabolized by two oxidative pathways, and the products of this type of metabolism are clinically insignificant when valproate is taken at therapeutic doses. These additional products of metabolism become much more important in supratherapeutic doses or intentional overdose. Under circumstances of acute ingestion, the role of these secondary oxidative pathways for drug elimination may be increased. These products are thought to be responsible for the constellation of symptoms described with acute intoxication.[8,9]

The first of these oxidative pathways, mitochondrial β-oxidation requires the presence of carnitine in order to move valproate molecules into the mitochondrial matrix from the cytosol via the "carnitine shuttle." Carnitine is derived both from dietary sources and, to a smaller degree, synthesis within the body.

The second oxidative pathway, cytosolic ω-oxidation, results in a variety of metabolites, among them 2-propyl-4-pentenoic acid (4-en-VPA) and propionic acid. These metabolites interfere with the urea cycle enzyme carbamoyl phosphate synthetase and leads to accumulation of ammonia. Clinically, this increased ammonia may present as valproate-related hyperammonemic encephalopathy, frequently noted in cases of valproate intoxication.[9,10]

Treatment

Carnitine Supplementation

In order to shunt valproate metabolism to mitochondrial β-oxidation, carnitine may be supplemented either orally or intravenously. Carnitine is administered in the form of levocarnitine (L-carnitine), the isomer of the molecule which is bioactive. Carnitine is available in the United States under the brand name Carnitor®, which is available as both oral and intravenous formulations. It is marketed for carnitine supplementation of carnitine deficiency due to inborn errors of metabolism and end-stage renal disease, and is used off-label for the treatment of valproate-related hyperammonemic encephalopathy.[10]

Although no hard indications exist for carnitine administration, it is generally recommended in cases of valproate toxicity with altered mental status or serum ammonia greater than 100 µg/dL. A typical dosage scheme is an initial dose of 100 mg/kg administered intravenously followed by 50-100mg/kg every eight hours until clearance of clinical toxidrome, normalization of ammonia levels, and demonstration of declining valproate levels. However, dosing guidelines are not well established as this is a relatively rare off-label use of carnitine, and pharmacy and toxicologist consultation is beneficial.[10,11,12] Carnitine administration is considered a relatively low-risk intervention,[13,14] with the potential for reversal of serious metabolic derangement.

Activated Charcoal

Activated charcoal use has been described in acute overdose, however it does not appear to decrease the concentration of valproate already absorbed into the blood stream. Its utility is limited to circumstances of recent ingestion in which it is believed that drug remains in the gut lumen.[15]

Naloxone

Case reports have described the use of naloxone in the reversal of acute valproate intoxication with observed clinical improvement in the depressed mental status. This has been attributed to naloxone's GABA inhibition, which counteracts valproate's GABA potentiation.[16] Naloxone does not address the mechanism of hyperammonemia caused by valproate intoxication.

Dialysis

Valproate is a dialyzable molecule, and severely intoxicated patients may require extracorporeal removal of the drug. Current consensus recommends dialysis in patients with a valproate level over 1300 µg/mL, signs of shock, or cerebral edema. Dialysis should be strongly considered in patients with a valproate level over 900µg/mL, coma

Valproate Toxicity
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Methemoglobinemia
continued from page 5

lengths differentially absorbed by hemoglobin and dexoyhemoglobin. MetHb absorbs light equally at both wavelengths, and when present at sufficient concentration, skews this ratio. As a result, conventional pulse oximetry will report a saturation of approximately 85% with significant methemoglobinemia, regardless of the actual blood oxygenation.[4] The partial pressure of oxygen reported on arterial blood gas analysis is unaffected by the presence of metHb, however, and a physiologically-appropriate paO2 with apparent hypoxemia on pulse oximetry is characteristic of methemoglobinemia.[2] When available, pulse co-oximetry – which measures light absorption at multiple wavelengths rather than the two of standard pulse oximetry – can be used to accurately and non-invasively assess metHb levels in real time.[12] The diagnosis of methemoglobinemia is confirmed via laboratory analysis directly measuring metHb levels.[1,11]

Management

Identification and withdrawal of the inciting agent is the primary treatment for methemoglobinemia. Otherwise healthy, asymptomatic patients with metHb levels <30% may need no further intervention beyond supportive care.[2,4] Similarly, infants with metHb <20% in the setting of dehydration may be managed with intravenous hydration alone.[4,5] Patients who are symptomatic, have evidence of tissue hypoxia (e.g., metabolic acidosis), or have metHb levels >30% should be treated more aggressively. Those with significant co-morbidities and poor physiologic reserve should be treated at metHb levels >10%, even if asymptomatic.[2,4] The first-line pharmacologic treatment for methemoglobinemia is intravenous methylene blue, which facilitates reduction of metHb to hemoglobin via the NADPH-metHb-reductase pathway. The initial dose is 1-2 mg/kg of a 1% solution given over 5 minutes, which may be repeated in 1 hour if necessary.[3] A continuous infusion may be indicated in refractory cases; however, toxic effects of methylene blue occur at doses >7 mg/kg.[2,3,6] Methylene blue is likely to be ineffective in patients with NADPH-metHb-reductase deficiency and G6PD deficiency, and may cause additional oxidative injury.[6] When methylene blue is ineffective, unavailable, or contraindicated, alternative therapies include red cell exchange transfusion and hyperbaric oxygen.[13,14,15]

Summary

Acquired methemoglobinemia is a potentially-fatal complication of exposure to an oxidizing agent, and should be considered in patients who present with cyanosis refractory to supplemental oxygen administration who do not have another cause of their hypoxia. Additional clinical findings that suggest the diagnosis include abnormal blood coloration, low peripheral oxygen saturation despite physiologically-appropriate PaO2 on blood gas, and historical features suggesting an oxidative exposure. Methemoglobinemia should be confirmed by co-oximetry or quantitative laboratory analysis. Standard treatment includes withdrawal of the inciting agent, supportive care, and intravenous methylene blue in severe cases.

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Long QT Syndrome
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that prophylactic administration of magnesium to patients requiring a QT-prolonging medication can decrease dysrhythmias and shorten the QTc, and this may be considered in patients with LQTS risk factors who absolutely require continued administration of QT-prolonging medications.[1]

A careful family history should be taken and patients should be referred to cardiology if there is concern for congenital LQTS. Beta blocker therapy, specifically propranolol and nadolol, has a proven mortality benefit in patients with congenital LQTS. If determined to be at high risk (*e.g.*, survivors of cardiac arrest, syncope despite maximum beta blocker therapy, QTc >550 ms), patients may require left cardiac sympathetic denervation and/or implantable cardiac defibrillator.[8]

LQTS may be congenital or acquired and is most often found on screening EKG, but occasionally presents as sudden arrhythmias or cardiac arrest. Providers must maintain a high index of suspicion and consider the diagnosis in all cases of syncope or cardiac arrest, particularly in the young patient. Treatment ranges from beta-blockade for the asymptomatic to ICD placement for those symptomatic. Avoidance of QT prolonging medications is also essential to prevent degeneration to Torsades or life threatening arrhythmias. Patients should be screened for electrolyte abnormalities and these should be aggressively corrected. LQTS is a life threatening condition and patients who presents with symptoms and a QTc greater than 500ms should be admitted for observation and further management, while those who are asymptomatic should have close follow up arranged.

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Testicular Torsion

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degrees of rotation with the goal of improving pain while arrangements are made for transfer to a facility that can provide definitive surgical care. Manual detorsion should be immediately terminated if the patient's pain increases, as this may actually make the torsion worse.[1,6]

Prognosis depends on time to detorsion after symptom onset and the overall degree of torsion. The recommended time window to avoid permanent ischemic damage is four to eight hours.[1,14] There may be irreversible damage to sperm formation after 4 to 6 hours of ischemia and testosterone production after 12 hours of ischemia.[2] The testicle salvage rate is 90-100% within 6 hours, 50% within 12 hours and below 10% after 24 hours of symptom onset.[1] Neonatal testicular salvage is much lower, between 9% and 22%. This is likely due to the lack of specific symptoms in neonatal presentations which often leads to delayed diagnosis.[16] Of note, unsalvageable testicular torsion's effect on fertility is not completely understood. Some studies show a decreased sperm count, decreased sperm motility, and abnormal morphologies, while other smaller studies show no significant difference.[15] Lastly, studies suggest that serum FSH, LH, and testosterone are within normal ranges for patients who underwent both orchiopexy and orchiectomy.[15] Testicular torsion remains a urological emergency and should always be considered on the differential when young males present to the ED with acute onset scrotal or lower abdominal pain.

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Valproate Toxicity

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without cerebral edema, respiratory depression requiring mechanical ventilation, or acidemia below a pH of 7.10. It should be noted that carnitine is also removed by hemodialysis; therefore, concurrent administration of these two therapies requires coordination between providers.[17]

Summary

Care for the patient suffering from an acute valproate intoxication requires high-suspicion as the clinical presentation is non-specific, with depressed mental status as the most frequent symptom. Laboratory evaluation for valproate levels and ammonia levels will help to identify this toxidrome and should be repeated to assess response to treatment and ensure clearance. While excellent supportive care is critical for these patients, there are specific interventions available to clinicians who have identified an acute valproate intoxication. The most important of these are intravenous carnitine, which decreases ammonemia by shunting metabolism of valproate away from urea-cycle blocking metabolites. Additionally, hemodialysis should be considered in severe toxicity because it removes valproate itself from the bloodstream. Valproate toxicity is an uncommon but not infrequent complication in patient's taking this medication for epilepsy, mood stabilization, or in an attempt at self-harm. Swift identification of this toxidrome by emergency physicians can lead to early disease-specific treatment and improved patient outcomes.

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Leprosy

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is an incredibly rare disease in the United States, but it can lead to devastating lifelong morbidity for patients. Emergency providers should be familiar with its presentation and initial management.

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EKG focus

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History of Present Illness

A 28 year-old male presents to the emergency department with reported seizure activity. The patient states that he was seated at his office desk when he felt palpitations and lightheaded just before the event. Witnesses report that the patient had eye-flickering and myoclonus of the extremities. The patient is of East Asian descent but was adopted as an infant and is unaware of any family history from biological parents. As part of his evaluation in the emergency department, an electrocardiogram is ordered.

Brugada Syndrome

Brugada syndrome is a sodium channelopathy that predisposes its victims to sporadic ventricular dysrhythmias, particularly ventricular fibrillation. These episodes often occur nocturnally and with rest, possibly stemming from increased vagal tone. The occurrence of Brugada syndrome has been linked to mutations in SCN5A, a gene that encodes the α-subunit of the cardiac sodium channel (INa); however, only 30% of patients with confirmed Brugada syndrome demonstrate a SCN5A mutation, suggesting a polygenic etiology. The disease is most prevalent in southeast Asian populations, particularly Japan and Thailand. Interestingly, phenotypic manifestations and genetic penetration is markedly more prevalent in male patients despite autosomal transmission of the SCN5A gene.

Several theories surround the exact pathophysiology underlying Brugada syndrome, its characteristic electrocardiographic changes, and the mechanism by which it predisposes its victims to ventricular dysrhythmias. Patients with Brugada syndrome al-

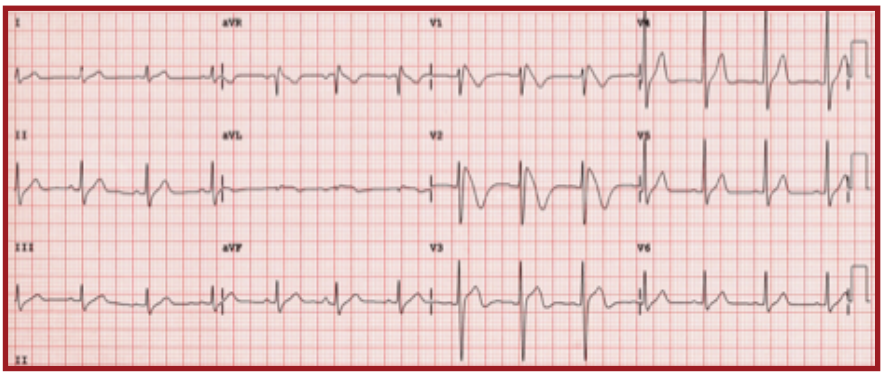

Image 5: Representative EKG of Brugada Syndrome

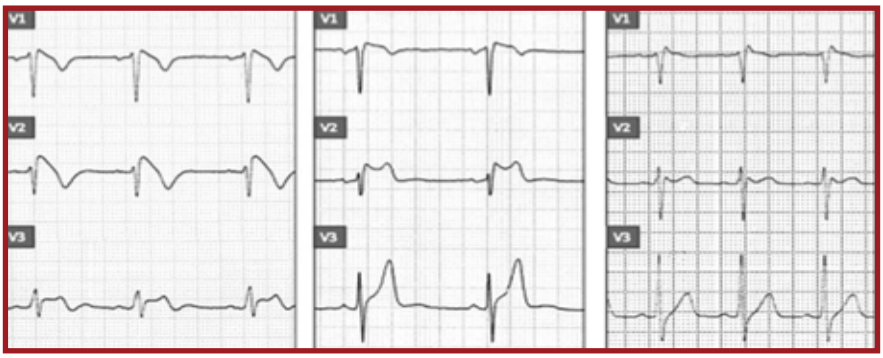

Image 6: Representative EKG comparing Brugada Types I, II and III

most invariably demonstrate fibrofatty changes to the myocardium. On histological examination, these changes are similar to the myocardial remodeling in arrhythmogenic right ventricular cardiomyopathy, and may precipitate and/or potentiate ventricular dysrhythmias. In contrast, some animal models suggest that transient outward potassium rectifier channels are present in greater numbers in the epicardium in comparison to the endocardium. Defects in INa function, in turn, may exacerbate this physiologic "transmural voltage gradient," leaving the epicardium more susceptible to aberrant depolarization.

The electrocardiographic features of Brugada are demonstrated above. Brugada syndrome manifests as J-point elevation with either a coved-type ST-segment morphology and negative T-wave impulse (type 1) or a saddleback ST-segment morphology (type 2). Recently, a third morphology has been described, wherein patients demonstrate either Type 1 (coved) or type 2 (saddleback) changes without ST-segment or J-point elevation (type 3). Type 1 morphology is essentially diagnostic of the disease, though type 2 and type 3 typically require confirmation with provocative testing (specifically, sodium channel blockade). Patients with Brugada syndrome often also demonstrate a right bundle branch block. Brugada syndrome is managed by the placement of an implantable cardioverter-defibrillator.

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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.

Submitted B Pod Cases

Case	Providers
Ethambutol Toxicity	Hunt/Bryant
Capsular Warning Syndrome	Golden/Baxter
Aortic Dissection	Ventura/Ryan
Polycythemia	Laurence/Knight
Methemiglobinemia	Gauger/Roche
Hypertrophic Cardiomyopathy	Shaw/Ronan