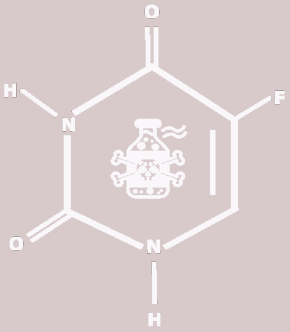
University of CINCINNATI Emergency Medicine

ANNALS OF B POD

Winter 2022 (Volume XVI Issue II)

Leadership Excellence Opportunity



8

5-FU Toxicity

by:

Josh Ferreri, MD

10

Human Trafficking

by:

Bailee Stark, MD

12

Hyperkalemia with Sine Wave

by:

Tony Fabiano, MD

Milk-Alkali Syndrome

Author: Olivia Gobble, MD
University of Cincinnati R2

Editor: Marlena Wosiski-Kuhn, MD
University of Cincinnati R3

History of Present Illness

A male in his 50s presents with concern for alcohol withdrawal. He endorses being on a "bender" over the last six days, drinking approximately 12 vodka mixed drinks and several glasses of wine a day, with his last drink occurring at 9pm yesterday evening. He had been sober from alcohol for the past eight months while taking care of his terminally ill brother, but his brother recently died, prompting his alcohol intake. He states he has previously been hospitalized for alcohol withdrawal but denies any history of withdrawal seizures. He endorses tremulousness, agitation, anxiety, headache, nausea, and several episodes of vomiting, increasing in severity over the last eight hours. He has taken about "one full bottle" of Tums over the past two days due to abdominal discomfort.

T 98.4

HR 160

BP 111/70

RR 16

96% ORA

Past Medical History
Alcohol Use Disorder

Past Surgical History
None

Past Social History
Significant alcohol use (typically vodka drinks and wine)
Drinks 6-8 drinks per day when drinking
No tobacco or recreational drug usage

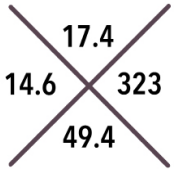
Medications
None

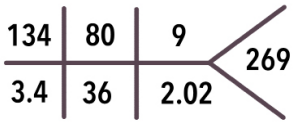
Allergies
Amoxicillin

Physical Exam

Patient is an anxious and generally unwell appearing gentleman. He is awake, alert, and oriented. He is tachypneic, with clear breath sounds bilaterally and no wheezing or crackles. He is tachycardic with a regular rhythm and no appreciable murmurs. His abdominal exam is unremarkable. He has numerous bruises in various stages of healing, primarily distributed over his bilateral lower extremities. He also has fast speech and tremors of the bilateral upper extremities at rest, with no signs of asterixis. There is no evidence of cranial nerve, motor, or sensation deficits.

Labs and Imaging





Lactate 3.7, repeat lactate 2.3 (2 hrs later, following 1L IVF)
Ca 16.4, Mag 1.0
Free Calcium 7.18 (4.40-5.40)
PTH 10.0 (12.0-88.0)
pH 7.56, PCO2 51, HCO3 46, Base Excess 19.9
CK 646

Hospital Course

The patient's presentation was initially concerning for alcohol withdrawal and initial Clinical Institute Withdrawal Assessment (CIWA) Score of 24 prompted administration of multiple rounds of intravenous and oral benzodiazepines with some improvement of vital sign abnormalities and symptoms. Nephrology was consulted from the emergency department given electrolyte abnormalities and significant hypercalcemia. They recommended aggressive rehydration and admission for further management. The patient received two liters of normosol within the emergency department with some improvement of lactate (3.7 to 2.3), creatinine (2.02 to 1.45), and free calcium (7.18 to 6.66). His potassium (K) was also repleted. Upon admission, his CIWA was 4 and he was placed on a standardized CIWA protocol. He received an additional two-liter fluid bolus and then was started on continuous IV fluids (IVF) running at 75 ml/hr. He was also given 80 milligrams of furosemide. His vitamin D levels on admission were 18.4 (normal limit 30.0-100.0). Vitamin D supplementation was held during admission as the patient was receiving benzodiazepines which can alter Vitamin D metabolism. On the second day of admission, creatinine (Cr) had improved to 1.17 and IV fluids were discontinued. However, at this time his phosphorus was also noted to be low; this was thought to be secondary to refeeding syndrome.

His calcium (Ca) continued to improve, with levels of 8.6 on day two of hospitalization. The patient remained hemodynamically stable with improvement of his electrolyte derangements and symptoms of withdrawal and he was medically ready for discharge after a three-day admission. He was discharged on a multivitamin for his vitamin D deficiency and recommended to follow-up with his primary care physician.

Discussion

History and Epidemiology

Milk-alkali syndrome (MAS) is typically characterized by the triad of hypercalcemia, metabolic alkalosis, and acute kidney injury. First described in 1923, it was thought to be a reaction to the "Sippy Regimen," an hourly administration of "milk-and-bicarbonate-containing" salts

that was used in the treatment of peptic ulcer disease. However, since the advent of nonabsorbable antacids and histamine blockers in the 1970s, the prevalence of this condition significantly decreased.[1] More recently, cases of MAS are often associated with older women who have been taking calcium supplementation in the setting of osteoporosis.[2]

In 2005, Picolos et al performed a retrospective review of the prevalence of MAS in patients admitted at a University Hospital between November 1998 and October 2003 for management of hypercalcemia without a history of end stage renal disease (ESRD). This study found that MAS was the third leading cause of hypercalcemia in hospitalized patients without ESRD and the second leading cause in cases of severe hypercalcemia, defined as corrected serum calcium of 3.5 mmol/L or higher. The correct diagnosis was mentioned in the chart in less than half of the cases, indicating that MAS is likely often under or misdiagnosed.[3]

Demographics and Risk Factors

MAS has been found to have a female predominance, with female to male ratio of 8:3. It is theorized that this predominance is explained in part by increased public awareness of osteoporosis in post-menopausal women and the role of calcium carbonate in its prevention and treatment. In addition to osteoporosis, chronic kidney disease, peptic ulcer disease, gastroesophageal reflux, and gastritis are also risk factors for the development of MAS, as they are associated with ingestion of calcium carbonate.[3]

Pathophysiology

Hypercalcemia develops in one of three basic mechanisms: increased intestinal absorption, increased bone resorption, or decreased urinary calcium excretion.[4] The pathophysiology of MAS is complex, but in general can divided into two phases: generation and maintenance. Factors involved in the generation of the hypercalcemia include increased intestinal absorption, inability for bone buffering due to saturation of calcium and decrease in renal excretion. After elevated calcium levels have been produced, these elevated levels are maintained via multiple mechanisms: volume depletion from diuresis as activated by hypercalcemia, a decrease in glomerular filtration rate (GFR) which reduces the filtration of calcium, and increase in renal reabsorption of calcium which is itself a result of the metabolic alkalosis and volume depletion.[2]

Symptoms and Diagnosis

The symptoms of MAS on initial presentation vary by the amount and duration of calcium ingestion, as well as the presence of risk factors such as concomitant thiazide diuretic usage.[5] Table 1 summarizes the differences between the classical and modern presentations, as well as the differences between the three classical subtypes. In the classical presentation based on patients who presented following initiation of the "Sippy Regimen," symptoms would vary based on the amount of milk and alkali ingested and over what time course, with three different subtypes of acute, subacute, and chronic. The acute subtype typically presented after one week of treatment and symptoms were typical of acute hypercalcemia: nausea, vomiting, weakness, and altered mental status. The chronic subtype most commonly presented with polyuria, polydipsia, muscle aches, and pruritis. Often, there was also evidence of diffuse calcifications, such as band keratopathy and nephrocalcinosis. Although initial lab work was similar between these subtypes, the amount of kidney function recovered after removal of offending agents differed, with chronic subtypes frequently having significant long-term kidney dysfunction.

Classical Presentation			
	Acute	**Subacute**	**Chronic**
Etiology	Complication of treatment with milk and alkali with symptoms seen between 2 and 30 days (typically after 1 week)	Ingestion of milk and alkali that occurs intermittently over years	Long history of high milk or alkali ingestion over many years
Symptoms	Nausea, vomiting, weakness, myalgias, irritability, headache, mental changes (psychosis)	Nausea, vomiting, mental changes , polydipsia, polyuria	Muscle aches, pruritis, polydipsia, polyuria, abnormal clacifications including band keratopathy and nephrocalcinosis
Typical lab findings	Elevated Ca, BUN and creatinine; normal or elevated phosphorus; possible metabolic alkalosis		
Response to withdrawal	Rapid relief of symptoms and return of renal function	Rapid relief of symptoms; gradual but significant improvement of kidney function	Slow improvement of muscle aches and pruritis; little to no improvement of renal function
Sex	Predominantly male		
Modern Presentation			
Etiology	Calcium carbonate ingestion		
Symptoms	Often asymptomatic, but may present with symptoms of acute hypercalcemia (nausea, vomiting, weakness)		
Typical lab findings	Elevated Ca, BUN, and creatinine; normal or decreased phosphorus, normal or decreased magnesium; metabolic alklaosis; intact PTH generally reduced		
Response to withdrawal	Withdrawal of calcium carbonate generally produces improvement clinically and rapid improvement of hypercalcemia and metabolic alkalosis		
Sex	Predominantly female		

Table 1: Differences between the classical and modern presentation of Milk-Alkali Sydrome

Continued on page 14

POST-CHOLECYSTECTOMY Choledocholithiasis

Author: Alexis Kimmel, MD
University of Cincinnati R4

Editor: Kristin Meigh, MD
University of Cincinnati R4

History of Present Illness

The patient is a female in her 20's who presents to the emergency department with abdominal pain. She has past surgical history of recent laparoscopic hysterectomy one month prior for abnormal uterine bleeding as well as recent cholecystectomy nine months prior for symptomatic cholelithiasis. She additionally has a history of systemic lupus erythematosus, seizure disorder, asthma, and obesity.

The patient states that she has been experiencing severe, diffuse abdominal pain which began three days ago and acutely worsened yesterday. This pain is associated with nausea and non-bloody, non-bilious emesis. She reports fever to 103°F and night sweats. She denies any melena or hematochezia. She denies dysuria, hematuria, or vaginal discharge. She has been taking ibuprofen for her symptoms without relief. When asked if she has experienced similar symptoms in the past, she reports that her pain today feels similar to the pain she experienced when she had her gallbladder removed.

Past Medical History

Systemic Lupus Erythematosus (SLE), asthma, obesity, epilespy

Past Surgical History

Cholecystectomy, laparoscopic hypsterectomy, laparoscopic bilateral tubal ligation

Medications

Acetaminophen, albuterol, aspirin, famotidine, hydroxychloroquine, ibuprofen, levetiracetam, mometasone-formoterol, naproxen, ondansetron, polyethylene glycol, promethazine, scopolamine, senna-docusate, simethicone

Allergies

Amoxicillin, latex

Past Social History

Denies alcohol, tobacco, or illicit drug use

T 99.1 F	HR 72	BP 127/69	RR 19	99% on RA

Physical Exam

The patient is well-appearing and in no acute distress. She has moist mucous membranes with no conjunctival injection or scleral icterus. She has diffuse abdominal tenderness to palpation which is most significant in the right upper quadrant. She has no guarding, rebound tenderness, or rigidity appreciated on exam. No costovertebral angle tenderness. The heart and lungs are clear to auscultation. She has strong pulses in all extremities without peripheral edema. The skin is dry without rashes or jaundice. There are no focal neurologic deficits.

Labs and Imaging

	12.4	
7.2		266
	39.9	

140	102	9	94
3.7	27	0.72	

Tbili 0.8, Direct Bili 0.4, Indirect Bili 0.4
AST 165, ALT 100, Alk Phos 110
Lipase 36
Lactate 1.8
UA notable for proteinuria, ketonuria, and urobilinogen
CT scan of abdomen and pelvis was notable for mild fat stranding adjacent to the pancreatic head in the region of the porta hepatis

Hospital Course

Given that biliary pathology could not be excluded, the patient was admitted to the emergency department observation unit with a plan for magnetic resonance cholangiopancreatography (MRCP). Hepatic panel was repeated approximately 13 hours after presentation to the emergency department and the patient was noted to have an increase in serum

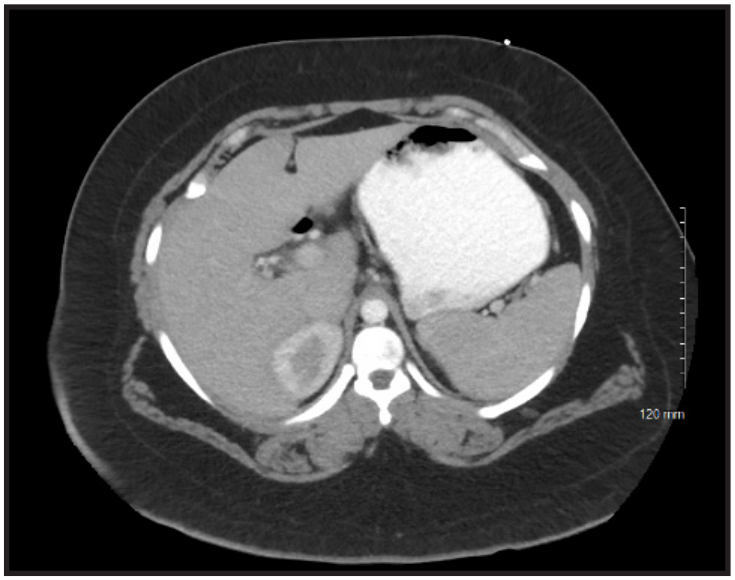


Figure 1: Representative image of axial CT scan demonstrating fat stranding in the region of the porta hepatis

transaminases (AST 442, ALT 400) and an elevated total bilirubin at 1.8 mg/dL with direct bilirubin elevated to 1.34 mg/dL. On the first day of her hospitalization, the patient underwent MRCP which was notable for choledocholithiasis. (Figure 2) The gastroenterology service was then consulted and performed endoscopic retrograde cholangiopancreatography (ERCP) on the third day of hospitalization. During the procedure, a 4-5 millimeter stone was removed from the common bile duct. Patient reported improvement in pain and nausea post-procedurally and laboratory studies demonstrated improvement in transaminases and hyperbilirubinemia. Patient was discharged shortly after without complication.

Discussion

Pathophysiology, Clinical Presentation, & Epidemiology

The term post-cholecystectomy syndrome (PCS) is used to describe persistence of symptoms of biliary colic in patients who have undergone cholecystectomy. These symptoms include episodic right upper quadrant pain, fatty food intolerance, nausea, and vomiting, among others. This often occurs in the immediate post-operative period but can occur even months to years after cholecystectomy.[1] The etiology of PCS can be multifactorial; causes range from extrabiliary pathology such as pancreatic masses to biliary etiologies such as retained gallstones or sphincter of Oddi dysfunction. Patients with post-cholecystectomy choledocholithiasis (PCC) will similarly present with many of the signs and symptoms of PCS.

Acute cholangitis is an infection of the extrahepatic biliary tract caused by obstruction of the biliary ducts, with the most common cause of obstruction being choledocholithiasis.[2] The obstructing gallstones can be retained or recurrent. Beyond gallstones, other causes of post-cholecystectomy common bile duct obstruction include iatrogenic causes such as migratory surgical clips.[3] The diagnosis of acute cholangitis can be made in a patient presenting with abdominal pain, fever, and jaundice—the classically described "Charcot's Triad"—however this constellation of signs and symptoms has a very poor sensitivity for the disease process of approximately 26 to 36 percent.[2,4] Furthermore, the presence of Reynold's pentad, which encompasses the above symptoms as well as hypotension and altered mental status, has an even lower sensitivity for cholangitis, with one analysis estimating only 4.8%.[4] One must therefore carry a high suspicion for the disease process in patients presenting with right upper quadrant pain and other PCS symptoms, as the absence of classic laboratory and physical exam findings can make the condition difficult to diagnose.

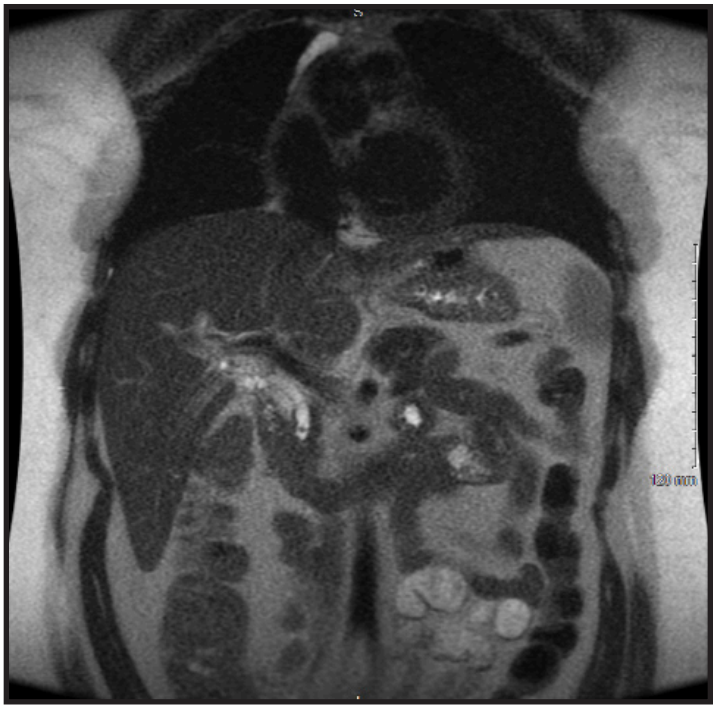


Figure 2: Representative coronal image of patient's MRCP demonstrating choledocholithiasis

The diagnosis remains important to keep on the differential, as many common bile duct (CBD) stones remain symptomatically silent or undiagnosed at the time of cholecystectomy despite techniques such as intra-operative cholangiography to detect them. The incidence of post-cholecystectomy choledocholithiasis diagnosed at least two months post-operatively was estimated at 1.84% in a retrospective single-center study conducted on over two thousand patients from 2007-2014.[5] Another study investigated risk factors of late development of post-cholecystectomy choledocholithiasis, where late development was defined as greater than 6 months after the surgery.[6] These risk factors included presence of acute cholecystitis at time of cholecystectomy, old age, periampullary diverticulum, and the presence of gallstones less than 0.55 centimeters.[6] The time to development of PCC is variable, with most occurring in the initial months to years post-cholecystectomy though the presentation can be delayed; case reports have documented PCC decades after the initial surgery.[7]

Diagnosis

The laboratory pattern in choledocholithiasis typically shows an initial rise in serum transaminases with a delayed direct hyperbilirubinemia and rise in alkaline phosphatase, as was seen in this patient.[8,9] Patients whose pathology has progressed to cholangitis may have accompanying laboratory evidence of infection, such as leukocytosis with neutrophilia. Those who have developed sepsis may demonstrate elevated lactate with anion gap metabolic acidosis and evidence of end-organ dysfunction secondary to infection with positive blood cultures.

In a patient in the emergency department with suspected choledocholithiasis, the initial imaging test of choice is a bedside transabdominal ultrasound of the right upper quadrant of the abdomen to assess for the presence of gallstones or a dilated common bile duct. Of note, patients who are post-cholecystectomy may have a dilated common bile duct on ultrasound even in the absence of mechanical obstruction.[10] CBD dilation up to ten millimeters may be considered normal in the post-cholecystectomy population, while further dilation is thought to be suggestive of obstruction.[1] Unfortunately, transabdominal ultrasonography only has a sensitivity of approximately 70-73% in detecting choledocholithiasis due to its inability to visualize the extrahepatic biliary tree in its entirety.[8,10,11] CT is also noted to have low sensitivity in detecting this pathology, with estimates around 70%.[12] Therefore, in a patient with high clinical suspicion for choledocholithiasis and a negative ultrasound and/or CT, cholangiographic imaging with MRCP or ERCP with endoscopic ultrasonography (EUS) should be performed.[10]

MRCP is a type of magnetic resonance imaging which performs non-invasive assessment of the hepatobiliary system and pancreatic ducts. ERCP differs from MRCP in that it is both diagnostic and therapeutic. This procedure entails cannulating the ampulla of Vater and CBD with injection of contrast under fluoroscopy and observing for filling defects.[8] Stones can then be endoscopically retrieved if visualized during this procedure. Another technique, endoscopic ultrasonography, is an imaging modality typically performed by a gastroenterologist and involves placement of the ultrasound transducer endoscopically into the second part of the duodenum. This allows for improved visualization of the biliary tree by avoiding bowel gas, which can limit the sensitivity

Continued on page 15

5-FU TOXICITY

Author: Josh Ferreri, MD
University of Cincinnati R3

Editor: Bailee Stark, MD
University of Cincinnati R3

History of Present Illness

An elderly female patient presents to a community emergency department from her outpatient oncologist office due to concerns of chest pressure. She has a diagnosis of metastatic colon cancer to the liver status-post percutaneous needle biopsy complicated by liver hematoma recently started on FOLFOX chemotherapy which contains leucovorin calcium (folinic acid), 5-fluorouracil (5-FU), and oxaliplatin. Past medical history is notable for pulmonary embolism and she is currently on apixaban. The patient endorses chest pressure over her center chest with radiation to her left shoulder which started while receiving a chemotherapy infusion. On chart review, the patient's chest discomfort began shortly after the patient's 5-FU infusion pump was being disconnected.

On arrival, the patient states her symptoms had resolved and she denies any persistent chest pain or chest pressure. She denies pleuritic, exertional, or positional symptoms as well as orthopnea or paroxysmal nocturnal dyspnea. She endorses baseline shortness of breath and dyspnea on exertion which is unchanged today. She denies any recent fevers, myalgias, or chills. She notes nausea that morning which resolved with her home promethazine and Zofran and denies abdominal pain or vomiting.

Past Medical History

Hypertension, hyperthyroidism, colon cancer with metastasis to the liver, pulmonary embolism, arthritis, anxiety, osteoporosis

Past Surgical History

Tonsillectomy, appendectomy, left sided partial thyroidectomy

Medications

Apixaban, aspirin, atorvastatin, citalopram, pantoprazole, isosorbide mononitrate, lisinopril, verapamil, potassium chloride

Allergies

Penicillins

Social History

5 pack-year smoking history (quit 2 years ago)
Infrequent alcohol use
Marijuana use
Denies use of recreational drugs

Family History

No known family history of diabetes, hypertension, or autoimmune disease

T 98.1 F	HR 73	BP 133/75	RR 16	99% on RA

Physical Exam

The patient is in no acute distress and is lying in bed comfortably without diaphoresis. She is somewhat hoarse. Head is normocephalic and atraumatic. Pupils are equal and reactive to light, and extraocular movements are intact bilaterally. There are no significant findings on ear, nose, and throat examination. Cardiopulmonary examination demonstrates regular rate and rhythm without murmurs, rubs, or gallops; lungs demonstrate rhonchi in the right lower lung base without rales or wheezing. There is no reproducibility of the pain on palpation of her chest. Her abdomen is soft and nontender without peritoneal signs. She has no rashes, ecchymosis, cyanosis, or edema on skin examination. She is alert and fully oriented with intact cranial nerve examination and equal movement of all extremities.

Labs and Imaging

	14.9	
4.2		270
	34.1	

140	103	17	
			121
3.5	25	0.60	

Calcium 9.4, Magnesisum 2.30, Phosphorus 2.6
Uric acid 6.7
Lactate dehydrogenase 241
Troponin <0.01
BNP 627

Bedside transthoracic echocardiogram. No evidence of pericardial effusion. Normal ejection fraction without significant evidence of RV systolic dysfunction
Chest X-ray: Linear atelectasis in the right lung base. Intrathoracic goiter on the left deviating the trachea to the right
CT soft tissue neck with contrast: Left vocal cord paralysis, probably due to severe multinodular goiter predominantly involving the left thyroid lobe
CT pulmonary angiogram: Decreased size of a chronic PE in right lower lobe. Extensive hepatic metastatic disease with decreased size of perihepatic hematoma. Multinodular goiter with extension on the left.

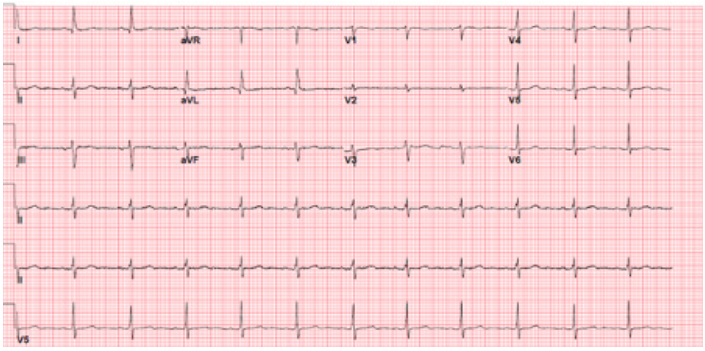


Figure 1: EKG on presentation to the ED

Hospital Course

Given the patient's history of recently diagnosed metastatic colon cancer as well as pulmonary embolism on therapeutic anticoagulation, the providers were concerned for worsening pulmonary emboli or progression of her metastatic disease contributing to her underlying pain. Her CT was negative for worsening thrombotic disease and there was no evidence of other acute cardiopulmonary process. She was found to have a large thyroid mass with normal thyroid studies. Otolaryngology was contacted and the patient was deemed an appropriate candidate for outpatient follow up. Though her BNP was elevated, her bedside echo did not show evidence of significant left ventricular systolic dysfunction. Providers also considered tumor lysis syndrome; however, her laboratory evaluation was inconsistent with this. Given the above, she was deemed appropriate for discharge with the underlying cause of her chest pain thought to be a combination of persistent pain from her chronic pulmonary emboli with a possible musculoskeletal component and/or anxiety. As the patient was preparing for discharge, she endorsed a recurrence of her chest discomfort. She described the pain as a sharp, pressure-like pain on the left side of her chest. A repeat EKG was obtained and revealed progressive EKG changes, as shown below. Most notably, the repeat EKG showed new ST elevations in leads I and aVL, ST depression in V1, and T wave inversions in reciprocal leads, namely leads V2 and V3. The cath lab was called immediately while the patient was given 324 mg aspirin and started on a heparin drip per ACS protocol. The patient was taken by interventional cardiology for emergent left heart catheterization, which ultimately revealed normal coronary vasculature without significant coronary artery disease. Cardiology recommended that the patient be treated with nitrates and isosorbide for further management for suspected coronary vasospasm. After thorough evaluation, it was suggested that her coronary vasospasm was likely secondary to 5-fluorouracil, which was discontinued during admission. She was started on verapamil and isosorbide for coronary vasospasm and discharged 3 days later in stable condition with cardiology follow-up.

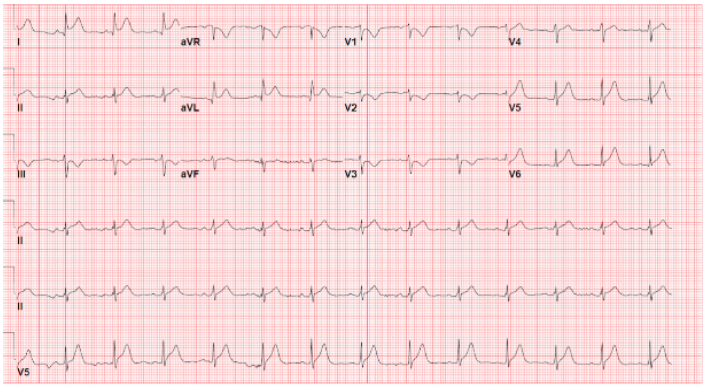


Figure 2: Repeat EKG with progressive changes

Discussion

Clinical Presentation

Much like our patient's presentation, 5-FU related coronary vasospasm presents similarly to any other patient experiencing cardiogenic chest pain. The most common side effect associated with 5-FU administration is angina,[1-4] however, many of these patients present asymptomatic with "silent ischemia" or "silent myocardial infarctions."[2] In these cases, patients are found to have ST elevation or other significant electrophysiologic changes concerning for myocardial infarction (MI) without symptoms. Asymptomatic EKG changes have been noted in up to 68%-88% of patients receiving 5-FU.[5-7] Other cardiac effects include bradycardia,[8] QT-prolongation and ventricular dysrhythmias,[3,9,10] acute heart failure,[11,12] and myocarditis.[13,14] Multiple case reports have found that these patients often present with chest pain that begins either during or shortly after their initial dose or infusion of 5-FU.[1,15] In many cases, troponin and other cardiac enzymes are normal on presentation,[1] further complicating diagnosis and management.

Epidemiology & Pathophysiology

A chief complaint of chest pain carries with it a broad and extensive differential diagnosis. Chemotherapy patients are especially high risk for many serious cardiopulmonary pathologies. After a thorough evaluation of the patient above, it was hypothesized that 5-FU-induced coronary vasospasm was the cause of her symptoms.

5-FU is a pyrimidine analogue that acts as a cytotoxic compound via its multiple metabolites. Specifically, it leads to termination of transcription and translation.[7,16,17] 5-FU is a component of many chemotherapeutic regimens including FOLFOX, a common colorectal chemotherapy regimen. Multiple studies have found an association between 5-FU and coronary artery vasospasm.[15,18-24] The risk of cardiovascular events ranges between 1.2-18.0% with risk of mortality between 2.2- 13.3%,[1,15] with some studies estimating the incidence of such adverse phenomena reaching upwards of 68%.[25,26]

The underlying mechanism of coronary vasospasm secondary to 5-FU has been debated for decades. Some studies propose direct endothelial damage by 5-FU leads to increased endothelial nitric oxide synthase activity, causing increased coronary vasospasm via protein kinase-C activity.[27,28] This hypothesis is further supported by a study conducted by Mosseri, et al in 1993 where patients who received Staurosporine (a protein kinase-C inhibitor) prior to 5-FU infusion had reduced risk of coronary events.[29] Similarly, some suggest that it is the increase in endothelin-1 production that promotes coronary vasospasm.[27,30] Endothelin-1 is a vasoconstrictor that is produced directly by endothelial cells. Some studies have found that both endothelin-1 as well as its precursor protein are elevated in patients receiving 5-FU who have experienced coronary events.[31]

Although coronary vasospasm has been among the most consistently reported cardiovascular side effect of 5-FU, additional cardiotoxic effects have been suggested including myocardial infarction, cardiomyopathy, electrophysiologic dysfunction at both the sinoatrial and atrioventricular nodes, and QT-prolongation.[9]

Cardiac Manifestations of 5-FU Toxicity
ST and T wave changes
Bradycardia
QT-prolongation
Ventricular dysrhythmias
Reduced EF
Myocarditis

Table 1: 5-FU effects on the heart

Management

Most medications used in the management of 5-FU induced cardiotoxicity have been aimed at the risk reduction and treatment of coronary vasospasm. Calcium channel blockers and nitrates have been used to treat those with vasospastic ischemia, as well as used as pretreatment in those who are thought to be at higher risk of vasospastic phenomena.[21,32] Notably, one study has found that the use of prophylactic nitroglycerin does not prevent EKG changes associated with 5-FU use.[33] Overall,

Continued on page 15

HUMAN TRAFFICKING

Author: Bailee Stark, MD
University of Cincinnati R3
Editor: Kristin Meigh, MD
University of Cincinnati R4

Case Presentation

A middle aged female is brought to the emergency department by police for altered mental status. Per police report, the patient was running away from them in the woods. Her behavior is erratic and she does not provide a succinct history. She describes visual hallucinations and makes odd statements throughout her interview. She does admit to methamphetamine use but does not provide further details. Her vital signs are within normal limits. She appears anxious on physical exam but does not have any focal physical exam abnormalities.

Social work later interviews the patient. Patient reports that she is currently being trafficked. She reports being forced to take illicit drugs as well as makes comments suggesting physical and sexual assault. Patient notes that she was initially trafficked in another state in the south where she became involved in a program for survivors of human trafficking. She was eventually offered housing in a rural area nearby because of this program. Unfortunately, the patient recently relapsed on methamphetamine and is being trafficked once again. Patient states that she is no longer safe in her current housing, which is located about 90 miles from the hospital

Social work was able to obtain collateral information from the program for survivors of human trafficking who confirmed the patient's report. The patient initially was welcome to return to her nearby safe house, however ultimately it was decided that the patient would return to her original safe house in the southern state, hundreds of miles away from the hospital's location. The patient remained in the emergency department a total of 33 hours with multiple services consulted prior to establishing a safe disposition plan.

Discussion

Human Trafficking

Human trafficking (HT) is defined as "the recruitment, transportation, transfer, harboring or receipt of people through force, fraud or deception, with the aim of exploiting them for profit."[1] While estimates vary, between 20-40 million persons worldwide are victims of trafficking, generating hundreds of billions of dollars in revenue.[2–4] HT is a social justice issue that is closer to home than many providers realize. Per a study performed by the Ohio Human Trafficking Task Force, over 1000 actively trafficked people were identified between 2013 and 2018 in Ohio with an additional 4000 persons identified to be at risk for trafficking.[5]

Healthcare providers are in a unique position to be able to identify, interact, and intervene for survivors of human trafficking. One national study reported that almost 90% of survivors of trafficking seek healthcare at some point, with over 60% of victims visiting an emergency department while they are being actively trafficked.[2,4,6] It is very important that emergency physicians are able to recognize signs of HT and can interact within their healthcare system to provide these survivors with the appropriate resources. While many guidelines have been suggested, there are no validated screening tools to detect survivors. To identify these patients, providers must be familiar with the signs, symptoms, and risk factors for HT all while maintaining a high index of suspicion. Once patients are identified, it is extremely important to use trauma-informed care practices to avoid re-traumatization and adequately connect these patients to the resources they need.

Trauma-Informed Care

Trauma is widespread and spares no demographics. Many of our patients have experienced significant trauma, and it is important for providers to appreciate how this can affect a person's health and healthcare utilization. Trauma has numerous deleterious effects on patients' physical and mental health and has been correlated to early mortality via a variety of mechanisms.[7] Trauma-informed care is defined as "a strengths-based service delivery approach that is grounded in an understanding of and responsiveness to the impact of trauma, that emphasizes physical, psychological, and emotional safety for both practitioners and survivors, and that creates opportunities for survivors to rebuild a sense of control and empowerment."

Four Rs of Trauma-Informed Care	
Realize	Understand and acknowledge the widespread nature of trauma
Recognize	Identify the signs and symptoms of trauma encountered in the emergency department
Respond	Utilize systems-wide policies and procedures to provide approrpiate care
Resist	Avoid re-traumatization by minimizing practices that could trigger emotions related to the original traumatic experience

Table 1. Trauma-Informed care principles

Substance Abuse and Mental Health Services Administration (SAMHSA) advises medical providers to make four key assumptions when providing trauma-informed care (Table 1). First, one must realize the widespread nature of trauma. Second, providers should be able to recognize that some patient behaviors, including agitation, irritability, anxiety, depression, sweating, flashbacks, difficulty concentrating, and self-blame, may be signs and symptoms of trauma. Next, providers must respond to patient trauma with policies and practices that are also trauma-informed to effectively connect the patient to the care they need. Finally, providers must be cautious to avoid re-traumatization in these already vulnerable patients.[8] Re-traumatization occurs when a situation that resembles a survivor's previous trauma triggers emotions related to the original traumatic experience. Providers can avoid re-traumatization by avoiding isolation, minimizing questioning, involving only necessary providers, and being sensitive to how certain environments, smells, or sounds could trigger a survivor.[8,9]

While trauma-informed care creates a safe environment for patients, many victims of trauma, including human trafficking survivors, will often

take multiple visits to feel comfortable disclosing their trauma to healthcare providers. Using this approach strengthens our patients' relationship to healthcare and encourages them to return to seek help and care in the future. [10]

Systems-Level Interventions

While a trauma-informed provider can provide excellent individual care to survivors of human trafficking in the emergency department, it is important to recognize limitations in the healthcare system. Though interventions at a systems-level may be difficult, these have potential to increase impact and are extremely important in providing care for survivors. According to a report published by the national anti-trafficking organization Polaris, "As with any enterprise, the business plan of a human trafficking venture is not built in a vacuum but rather exists within an ecosystem or matrix, depending on and intersecting with a range of legitimate industries and systems – cultural, governmental, environmental."[11] In 2017 Polaris conducted a survey to examine the intersection between HT and systems. The study included 127 persons that self-identified as a survivor of trafficking. Questions were asked about several systems and industries including the financial services industry, social media, transportation, hotels & motels, housing & homelessness systems, and health care. The study found that many survivors were significantly impacted by these systems in both positive and negative ways.[11] Knowing how these systems interact with HT can help us better identify barriers and propose interventions in this realm.

Our patient's case was fraught with systems-level issues. For example, it was exceedingly difficult to establish a safe disposition plan for the patient in our case due to barriers that existed between the healthcare system and the housing program in which she was enrolled. Unfortunately, housing insecurity and HT commonly overlap. In fact, 64% of survivors report homelessness or unstable housing prior to being trafficked. Furthermore, homeless shelters are a common recruitment location for trafficking with about 15% of survivors having been recruited directly from a shelter according to the Polaris study.[11] While availability of short-term shelters for victims is important, we must also focus efforts on preventing homelessness and educating persons involved in the housing system on how to recognize persons at risk. For example, Polaris noted that over half of survivors had contact with a landlord or rental office during the time that they were trafficked. By recognizing housing as a point of intervention for vulnerable people, we can identify ways to use the housing system to combat human trafficking including increasing funding for trauma-informed housing and shelter programs, training property owners on how to identify and respond to HT, and offering housing protections for HT survivors in lease agreements.[11]

Youth experiencing homelessness are particularly vulnerable to human trafficking with almost 20% of homeless youth having experienced human trafficking.[12] LGBTQ+ youth are even more at risk and are approximately five times more likely to engage in survival sex practices than their non-LGBTQ+ counterparts.[11] Prevention in these populations is imperative and includes offering job skills training, social media education, safety planning, partnerships with the juvenile justice system as well as creating spaces for particularly at-risk individuals including LGBTQ+ persons, male survivors, and individuals with disabilities.[11,13]

Another system that can alleviate or exacerbate trafficking is the judicial system. One study in Ohio found that more than 90% of women charged with prostitution-related offenses met the definition of human trafficking.[14] Charges related to prostitution, drug intoxication, and homelessness may actually be rooted in trafficking. Revisions must be made in the justice system to identify survivors of HT early to provide them with resources rather than incarcerate them and perpetuate the cycle of trafficking. Training law enforcement, prosecutors, and judges is essential to identifying and intervening for survivors. Additionally, the judicial system has the power to impact the demand side of HT by identifying and prosecuting traffickers. Fortunately, Ohio Attorney General Dave Yost made this a large focus of his work in 2019.[15]

Finally, we must recognize the unique intersection between the healthcare system and HT, especially within the emergency department. As mentioned earlier, nearly all survivors seek healthcare at some point, with over 60% of victims visiting an emergency department while being actively trafficked.[2,4,6] It is important for healthcare systems to have protocols in place to help identify victims and intervene when possible. All providers should be educated on resources that are available at their facilities and in their communities as well as how to connect patients to these services. Healthcare providers can also assist by providing empathetic trauma-informed care. It is essential to create an environment in which patients know they are safe to seek care if they are being trafficked or are trafficked in the future.

The impact of the intersection between systems and HT was clear in our case. Several organizations across multiple states were involved including the healthcare system, housing, law enforcement, and several social services organizations. Despite the efforts and good intentions of all these groups, a safe disposition plan was not able to be established until over 30 hours were spent in the emergency department (ED). Not only is this lengthy ED stay detrimental to our patients' wellbeing, but it is also very costly, especially with ED boarding at an all-time high. As can be seen from the examples listed above, upstream efforts to work at the systems level are necessary to prevent and alleviate human trafficking.

Summary

In our case, the providers were familiar with the signs and symptoms of human trafficking and recognized how these played a significant role in our patient's clinical presentation. By using a trauma-informed model of care, the providers were able to gain the patient's trust and reconnect her with her previous housing program.

Unfortunately, despite all efforts from healthcare providers and ancillary staff, our patient still did not get fully connected to the resources she needed. On chart review, it appears that the patient presented to another local hospital 3 days after discharge for medical clearance prior to going to the justice center for methamphetamine use and "engaging in prostitution." Patient was seen again one month later for "medical clearance" for a human trafficking program however it does not appear that she was directly reconnected with the program and was ultimately discharged and told to follow up as an outpatient. This was her last known encounter with the health system to date.

There are many flaws in our intersecting systems that led to this unfortunate outcome. People should continue to identify systemic interventions to combat this cycle and provide human trafficking survivors with the resources they need. Through trauma-informed care, human trafficking awareness, and systems level interventions, healthcare professionals can take a leading role in identifying and intervening in cases of human trafficking.

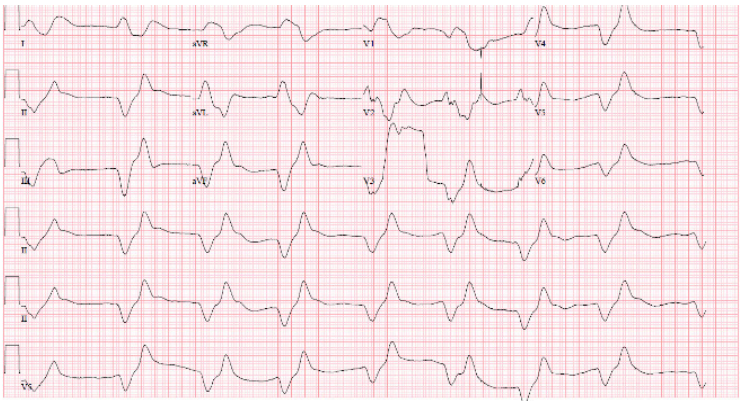
Continued on page 16

HyperKalemia With Sine Wave

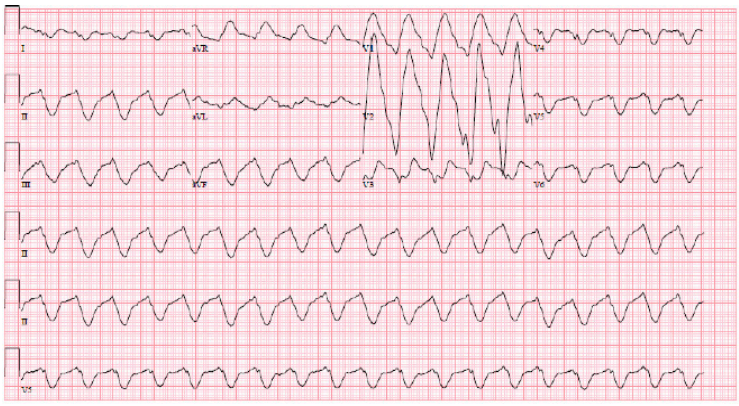
Author: Anthony Fabiano, MD
University of Cincinnati R3
Editor: Emily Roblee, MD
University of Cincinnati Alumnus

History of Present Illness

A female in her 30s with a history of end stage renal disease (ESRD) on dialysis presented to the emergency department (ED) for generalized weakness and shortness of breath for the previous day. Emergency medical services were called to the patient's house when she was too weak to get out of bed. She missed dialysis the day prior due to a clot in her dialysis graft. En route to the hospital, she was bradycardic to the 30s. On arrival to the ED she was also noted to be tachypneic and hypoxic on a non-rebreather. Once the patient was placed on the monitor she was noted to be in a wide-complex rhythm. An electrocardiogram (EKG) was obtained and is pictured below:



The patient was found to have a potassium of 10.1 mmol/L. She was given calcium gluconate, insulin, dextrose, and albuterol. She converted to a monomorphic ventricular tachycardia with a pulse, pictured below:



After treatment with amiodarone, the patient's rhythm began alternating between a wide complex tachycardia and sinus rhythm. Her potassium level decreased to 8.6 mmol/L. The patient was transferred to the medical intensive care unit where she received a trialysis line for emergent dialysis. She eventually underwent a declotting procedure for her dialysis graft and was discharged home in stable condition.

Discussiom

Background and Pathophysiology

Potassium is the most abundant intracellular cation in the human body but is relatively sparse in the extracellular environment. Under normal physiologic conditions, the difference in intracellular and extracellular potassium concentrations serves to establish the resting membrane potential of neurons, myocytes, and numerous other types of cells. Potassium homeostasis at the cellular level is maintained by Na-K-ATPase pumps, whereas potassium homeostasis of the whole body is maintained by the kidneys and adrenal glands via the renin-angiotensin-aldosterone-system (RAAS).[1,2] Although normally kept within a narrow physiologic range, potassium homeostasis can be affected by many diseases including diabetes, chronic kidney disease (CKD), heart failure, and RAAS-inhibiting medications (see table 1).[3-5] This makes hyperkalemia a common electrolyte disturbance encountered in the emergency department, with an estimated prevalence of 2.6-2.7% in the overall population and 8.9-9.3% in patients with CKD or heart failure.[3]

Risk Factors for Hyperkalemia
Chronic kidney disease (estimated glomerular filtration rate (GFR) <30)
Acute kidney injury
Heart failure
Diabetes mellitus
Severe tissue breakdown
Renin-angiotensin-aldosterone system inhibitors
Non-steroidal anti-inflammatory drugs
Potassium-sparing diuretics

Table 1: Red flags which should trigger awareness for the potential presence of hyperkalemia.

While there is no universal standard for the definition of hyperkalemia, the most widely accepted cutoff is a serum concentration of 5.5 mmol/L or greater.[4] The diagnosis of hyperkalemia is made via laboratory analysis but can also be suggested by changes on EKG. While EKG changes alone are not sensitive enough to be relied upon for diagnosis, they are not subject to lab error and are therefore more specific to true hyperkalemia. Interestingly, computer-driven analysis of EKGs has been shown to increase both the sensitivity and specificity of hyperkalemia recognition and diagnosis more rapidly and reliably than physician interpretation alone.[4,6]

There are numerous causes of hyperkalemia. Among the most common

is "pseudohyperkalemia" which results from cell lysis during phlebotomy or lab processing. Other causes include increased dietary intake (nearly impossible to achieve with normally functioning kidneys), and intracellular-extracellular shift due to acid-base disturbances. As little as a 2% shift of potassium can cause serum potassium levels of greater than 8 mmol/L.[2] The most common cause of clinically significant hyperkalemia, however, is impaired renal function.

Impaired renal function can result in hyperkalemia in multiple ways. Under normal circumstances, potassium is filtered at the glomeruli and reabsorbed in the proximal convoluted tubule with fine-tuning at the distal nephron. The gradient for distal potassium excretion is driven by sodium and water delivery and reabsorption. Decreased delivery of water and sodium to the distal nephron results in decreased ability to secrete potassium and subsequent hyperkalemia. This is why a patient with an oliguric acute kidney injury (AKI) may have transient hyperkalemia during the peak of their illness.[2] In the case of chronic kidney disease, decreased glomerular filtration rate (GFR) results in much the same phenomenon and once end stage renal disease (ESRD) develops, dialysis is required to prevent the development of hyperkalemia.

Classical Presentation

The clinically-significant consequences of hyperkalemia, which can be life-threatening, are related to its effects on the resting membrane potential of cardiac myocytes. In a normal physiologic state, large amounts of intracellular potassium create a negative resting membrane potential. When extracellular potassium concentration increases, the resting membrane potential of the cells becomes less negative, decreasing the cell's threshold for depolarization and resulting in increased myocyte excitability. A less negative resting membrane potential also means that fewer sodium channels are available to participate in depolarization, resulting in slower impulse conduction through the heart.[4,7] These changes result in a set of characteristic findings on EKG that frequently progress with increasingly elevated serum potassium, although it is important to note that they do not always correlate perfectly with the serum potassium and may occur in any order, or not at all. [4,7-9]

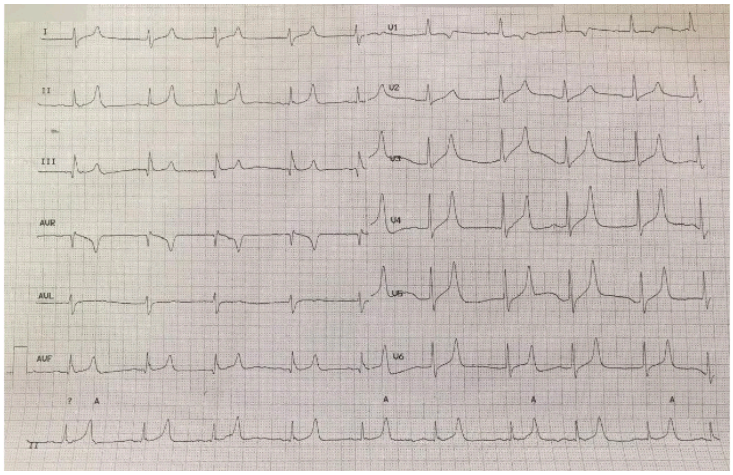


Figure 1: Peaked T waves in a patient with severe hyperkalemia

The classic first EKG change is a narrow based, peaked t wave, which results from increased ventricular repolarization (see figure 1). Peaked T waves can begin to appear when the serum potassium rises above 5.5 mEq/L. At levels above 6.5 mEq/L, changes in the resting membrane potential result in slower depolarization of the sinoatrial node pacemaker cell, and slower conduction through the atria. On EKG this results in flattening and widening of the p wave with elongation of the PR interval. Notably, these effects are seen in atrial conduction before ventricular conduction due to the atria's increased sensitivity to the current generated by potassium. As serum concentrations surpasses 7.0-7.5 mEq/L slowing of signal transduction begins to affect the ventricles and the His-Purkinje system. This manifests as intraventricular or atrioventricular conduction delays which distort and prolong the QRS and can progress to ventricular and junctional rhythms as atrial conduction fails entirely. This progresses to wide-complex bradycardia and development of a sine-wave pattern, which is a pre-terminal rhythm. Potassium levels above 8.0 mEq/L allow the atrioventricular node and ventricular myocytes to depolarize erratically leading to the development of ventricular tachycardia and ventricular fibrillation before progression to asystole and pulseless electrical activity (PEA).

Just as hyperkalemia exerts the above effects on cardiac myocytes, it can also affect other myocytes and neurons throughout the body. Hyperkalemia can cause peripheral muscle weakness, and there are multiple case reports of severe hyperkalemia even resulting in quadriplegia which resolves with normalization of extracellular potassium concentration.[7,10,11] Thus, acute hyperkalemia should remain on the differential diagnosis for any patient with appropriate risk factors and a chief complaint of weakness.

Treatment

There are very few randomized controlled trials for the acute management of hyperkalemia in the emergency department, and there is wide practice variation regarding the serum potassium level at which treatment of hyperkalemia is initiated.[14] Much of the data is retrospective, garnered from years of implementing treatments recommended by expert consensus guidelines and local practice patterns. The discussion of the treatments that follows is supported by the best and most current evidence available. [4,8,9,12-14]

Calcium

Calcium should be the first medication administered in hyperkalemia with EKG changes. The administration of calcium raises the threshold potential (potential needed for activation) making it more difficult to achieve depolarization. This results in the classically taught "membrane stabilization." Additionally, in cells with calcium-dependent action potentials, like cardiac myocytes, an elevated serum calcium results in a larger extracellular-intracellular calcium gradient, resulting in a larger inward calcium current, and increased signal conduction.[7,18] In total, this reduces the likelihood of ventricular early and late after-depolarizations and re-entry that can result in ventricular tachycardia and ventricular fibrillation. These beneficial effects can be seen even in normo-calcemic patients.

Intravenous (IV) calcium can come in either the form of calcium gluconate (which can be administered peripherally) or calcium chloride (which is administered centrally). It is worth noting that there is approximately 1/3 the amount of calcium in each 10 mL of 10% calcium gluconate (2.3 mmol) compared to each 10 mL of 10% calcium chloride (6.8 mmol).[4] Calcium chloride and calcium gluconate dissociate to produce free ionized calcium, resulting in rapid onset of stabilizing effects. However, the calcium then equilibrates and becomes mostly protein-bound, and can no longer translocate across the myocardial membrane to alter the myocardial threshold potential. This means that the effect of calcium is short-lived (~30-60 minutes) and requires frequent redosing.

Insulin and Dextose

Insulin administration lowers the extracellular potassium concentration by shifting potassium from the interstitium to the intracellular space. Insulin acts indirectly by stimulating the activity of the Na-K-ATPase pump on cells. The end result is re-establishment of the normal potassium gradient and return of the cell membrane potential closer to physiologic baseline. Dextrose is co-administered with the insulin to prevent hypoglycemia that would otherwise develop. Several studies

suggest that a dose of 10 units of IV insulin is noninferior to 20 units and results in less hypoglycemia. There is also some data to suggest that 5 units may be noninferior to 10 units. This therapy takes effect in approximately 10-30 minutes, peaks at approximately an hour, and dissipates by 4 hours. [4,9,13]

Albuterol

Similar to the mechanism of action of insulin, beta-2-adrenergic agonists such as albuterol indirectly stimulate increased activity of the Na-K-ATPase pump. The onset of action for decreasing serum potassium is within 15-30 minutes of administration with a duration of at least two hours.[15] There is some evidence to suggest that there is an additive effect with co-administration of insulin and beta-2-agonists.[4]

Bicarbonate

Sodium bicarbonate is also frequently used for patients with severe hyperkalemia. Hydrogen ions participate in cellular membrane exchange with potassium. The body attempts to compensate for acidemia by shifting extracellular hydrogen ions intracellularly in exchange for intracellular hyperkalemia. The administration of bicarbonate forces the body to reverse this exchange, pulling potassium into the cell and pushing hydrogen ions into the extracellular environment in an attempt to maintain pH. There is far less literature supporting this therapy, and the routine use of bicarbonate in treatment of hyperkalemia is controversial. The value in administration of bicarbonate in hyperkalemia is seen predominantly when there is concomitant acidemia.[1,4,9,15]

Renal Excretion

Thus far, all of the therapies discussed work to protect against the destabilizing effects of potassium, or shift it between fluid compartments. However, none of the discussed therapies have targeted removal of the excess total body potassium. While loop diuretics do not work immediately, if there is residual renal function, they may be given in the acute setting to increase the renal excretion of potassium within a few hours. Loop diuretics act on the Na-K-2Cl transporter in the distal nephron. To excrete potassium, the distal nephron requires appropriately high Na concentrations and thus sodium chloride may be given to facilitate higher total body sodium concentrations and further potassium excretion. It is also worth noting that sodium bicarbonate, as above, contains a significant amount of sodium and thus can help to facilitate potassium excretion through these means as well.[1,4,8,15]

GI Excretion

Potassium excretion in the GI tract can be facilitated by the use of potassium binders. These substances trap potassium in the gut lumen, preventing reabsorption and resulting in increased fecal excretion. Over the years there has been waxing and waning use of the GI tract as a method of total-body potassium elimination. This correlates with the advent of sodium polystyrene sulfonate ("Kayexelate") and the subsequent trials which have indicated a significant risk of bowel necrosis associated with its use.[4,9] Newer medications, such as sodium zirconium cyclosilicate ("Lokelma") have shown superior potassium binding and no associated risk of gut ischemia.[4,15-17] These are relatively new medications and their utility in the acute setting is being actively investigated, however, they appear to be very effective in binding and assisting with the excretion of potassium via the GI tract. The effects of these medications take several hours to several days to become apparent.

Dialysis

When all else fails, or there is a more emergent need to lower serum potassium, dialysis can be utilized. This can be performed via continuous renal replacement therapy (CRRT) or via intermittent hemodialysis (iHD). Emergent nephrology consultation is essential.

Treatment of Hyperkalemia	
Stabilization of the myocardium	Calcium
Intracellular shift of potassim	Insulin Albuterol Bicarbonate
Elimination of potassium	Loop diuretics Potassium binders Dialysis

Table 2: Treatment of acute hyperkalemia.

Summary

Hyperkalemia is a common electrolyte disturbance encountered in the emergency department, and can be life-threatening. Early, aggressive treatment which shifts potassium can help to stave off fatal cardiac arrhythmias until potassium elimination can be achieved. Swift management of these patients and appropriate disposition is essential for the emergency physician.

References

1. Palmer BF. A physiologic-based approach to the evaluation of a patient with hyperkalemia. American journal of kidney diseases. 2010 Aug 1;56(2):387-93.
2. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. Advances in physiology education. 2016 Oct 18.
3. Mu F, Betts KA, Woolley JM, Dua A, Wang Y, Zhong J, Wu EQ. Prevalence and economic burden of hyperkalemia in the United States Medicare population. Current Medical Research and Opinion. 2020 Aug 2;36(8):1333-41.
4. Lindner G, Burdmann EA, Clase CM, Hemmelgarn BR, Herzog CA, Małyszko J, Nagahama M, Pecoits-Filho R, Rafique Z, Rossignol P, Singer AJ. Acute hyperkalemia in the emergency department: a summary from a Kidney Disease: Improving Global Outcomes conference. European Journal of Emergency Medicine. 2020 Oct;27(5):329.
5. Montford JR, Linas S. How dangerous is hyperkalemia?. Journal of the American Society of Nephrology. 2017 Nov 1;28(11):3155-65.
6. Lin CS, Lin C, Fang WH, Hsu CJ, Chen SJ, Huang KH, Lin WS, Tsai CS, Kuo CC, Chau T, Yang SJ. A deep-learning algorithm (ECG12Net) for detecting hypokalemia and hyperkalemia by electrocardiography: algorithm development. JMIR medical informatics. 2020 Mar 5;8(3):e15931.
7. Campese VM, Adenuga G. Electrophysiological and clinical consequences of hyperkalemia. Kidney international supplements. 2016 Apr 1;6(1):16-9.
8. Ashurst J, Sergent SR, Sergent BR. Evidence-Based Management Of Potassium Disorders In The Emergency Department. Emergency Medicine Practice. 2016 Nov 1;18(11):1-24.
9. Bianchi S, Regolisti G. Pivotal clinical trials, meta-analyses and current guidelines in the treatment of hyperkalemia. Nephrology Dialysis Transplantation. 2019 Dec 1;34(Supplement_3):iii51-61.
10. Panichpisal K, Gandhi S, Nugent K, Anziska Y. Acute quadriplegia from hyperkalemia: a case report and literature review. The Neurologist. 2010 Nov 1;16(6):390-3.
11. Sanson G, Russo S, Iudicello A, Schiraldi F. Tetraparesis and failure of pacemaker capture induced by severe hyperkalemia: case report and systematic review of available literature. The Journal of Emergency Medicine. 2015 May 1;48(5):555-61.
12. Peacock WF, Rafique Z, Clark CL, Singer AJ, Turner S, Miller J, Char D, Lagina A, Smith LM, Blomkalns AL, Caterino JM. Real World Evidence for Treatment of Hyperkalemia in the Emergency Department (REVEAL–ED): A multicenter, prospective, observational study. The Journal of emergency medicine. 2018 Dec 1;55(6):741-50.
13. Moussavi K, Fitter S, Gabrielson SW, Koyfman A, Long B. Management of hyperkalemia with insulin and glucose: pearls for the emergency clinician. The Journal of Emergency Medicine. 2019 Jul 1;57(1):36-42.
14. Long B, Warix JR, Koyfman A. Hyperkalemia in the emergency department: yes, a need for further evidence, but do not discount what we have. Journal of Emergency Medicine. 2019 Jul 1;57(1):103-5.
15. Liu M, Rafique Z. Acute management of hyperkalemia. Current Heart Failure Reports. 2019 Jun;16(3):67-74.
16. Rafique Z, Liu M, Staggers KA, Minard CG, Peacock WF. Patiromer for treatment of hyperkalemia in the emergency department: a pilot study. Academic Emergency Medicine. 2020 Jan;27(1):54-60.
17. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, Roger SD, Yang A, Lerma E, Singh B. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. Jama. 2014 Dec 3;312(21):2223-33.
18. Parham WA, Mehdirad AA, Biermann KM, Fredman CS. Hyperkalemia revisited. Texas Heart Institute Journal. 2006;33(1):40.

Milk-Alkali Syndrome

Continued from page 5

Today, most MAS cases are secondary to the ingestion of calcium carbonate, rather than milk and alkali separately. Patients are often asymptomatic with hypercalcemia, alkalosis, and kidney injury found incidentally. Hypophosphatemia is also often present, as calcium carbonate has phosphate-binding properties and lacks the phosphate load that milk ingestion provides. Hypomagnesemia is also present due to the ability of hypercalcemia to inhibit magnesium reabsorption by the renal tubule. Finally, parathyroid hormone (PTH) levels are often decreased, secondary to suppression from the hypercalcemia.[6] Decreased PTH is an important distinguishing factor between MAS and hyperparathyroidism, as this is the only way to differentiate between the two apart from surgical exploration of the parathyroid glands and pathologic confirmation. However, it is important to be aware that there have been studies which found elevated levels of PTH in patients with MAS where surgical exploration later found normal parathyroid glands. This is thought to be due to issues with the PTH assay itself, with elevated

levels reading when the assay is measuring the carboxyl-terminal portion of PTH as opposed to amino-terminal assays that recognize the intact hormone. [7]

Treatment

Conventional treatment for MAS involves discontinuation of calcium and alkali ingestion along with aggressive volume repletion. In the emergency department, discovering the etiology, stopping additional calcium administration, and beginning fluid repletion are the main focus. After euvolemia has been achieved, there may be some benefit to gentle calciuresis via a loop diuretic, such as in the case presented here. Hypocalcemia, along with an accompanied rise in PTH, can often occur transiently after treatment with a loop diuretic. This is a unique reaction to MAS thought to be because cessation of calcium carbonate ingestion immediately removes the hypercalcemic stimulus, whereas suppressed PTH is often slower to respond.[7] This is also why treatment of MAS with bisphosphonates should be avoided, as they will cause a prolonged suppression of serum calcium.[3]

Summary

Milk-alkali syndrome is characterized by hypercalcemia, metabolic alkalosis, and acute kidney injury, most frequently caused by the ingestion of calcium carbonate. While initially considered rare since the advent of non-absorbable antacids and H2-blockers, the actual incidence is likely underestimated. Cases are more frequently seen in women and predisposing conditions include osteoporosis, peptic ulcer disease, and chronic kidney disease. Although often asymptomatic, it can present with symptoms of hypercalcemia such as nausea, vomiting, weakness, and muscle pains. The mainstay of treatment involves discontinuing calcium carbonate ingestion and aggressive fluid administration.

References

1. Abreo K, Adlakha A, Kilpatrick S, Flanagan R, Webb R, Shakamuri S. The Milk-Alkali Syndrome: A reversible form of acute renal failure. Arch Internal Medicine. 1993;153(8):1005-1010
2. Felsenfeld A, Levine B. Milk Alkali Syndrome and the Dynamics of Calcium Homeostasis. CJASN. 2006;1(4): 641-654.
3. Picolos M, Lavis V, Orlander P. Milk- Alkali Syndrome is a major cause of hypercalcemia among non-end-stage renal disease (non-ESRD) inpatients. Clinical Endocrinology. 2005;63(5):566-576.
4. Chonchol M, Kendrick J. Calcium Homeostasis in Kidney Disease. Endocrine Disorders in Kidney Disease. 2019:199-206.
5. Orwoll ES. The milk-alkali syndrome: Current concepts. Annals of Internal Medicine. 1982;97:242-248.
6. Medarov B. Milk Alkali Syndrome. Mayo Clin Proc. 2009;84(3):261-267.
7. Beall DP, Scofield RH. Milk Alkali syndrome associated with calcium carbonate consumption. Report of 7 patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. Medicine. 1995;74(2):89-96.

Post-cholecystectomy Choledocholithiasis

Continued from page 7

of transabdominal ultrasound for choledocholithiasis and other biliary pathology. In a small study of 155 patients with choledocholithiasis confirmed on ERCP, it showed that EUS was 96% sensitive as compared to transabdominal ultrasound (63%) and CT (71%).[12]

Intraoperative cholangiography can also be performed during cholecystectomy in order to evaluate for the presence of retained gallstones, however the data remains unclear as to whether this affects the rate of post-cholecystectomy biliary disease.[13] On record review, it does not appear that our patient underwent intraoperative cholangiography at the time of her cholecystectomy.

Management

Stabilization, symptom control, and specialist consultation are at the forefront of emergency department management once the diagnosis of post-cholecystectomy choledocholithiasis is suspected. Pain and nausea should be managed with analgesics and anti-emetics, respectively. If there is suspicion for ascending cholangitis with accompanying clinical findings such as fever, vital sign instability, or evidence of sepsis, fluid resuscitation should be initiated and antibiotics should be administered to include enteric coverage with medications such as piperacillin-tazobactam.[14] Early consultation is required for definitive management of the obstructing stone. This may still be pursued if clinical suspicion remains high in the setting of nondiagnostic imaging studies as the most widely available ED studies (CT and ultrasound) are often poorly sensitive in diagnosis of the disease.

The details of specific procedural and surgical interventions for stone removal are beyond the scope of this discussion. Endoscopic and minimally invasive techniques are generally preferred to open surgical techniques. ERCP is the most common method of removal, but carries a complication rate of up to twelve percent.[8] Laparoscopic removal is often complicated due to adhesive disease from prior cholecystectomy.[15] Lithotripsy may also be considered in select patients.

Summary

While choledocholithiasis in a patient status-post cholecystectomy remains rare, providers in the emergency department must have a high degree of suspicion for this pathology, especially in patients at increased risk. If suspected, a bedside right upper quadrant ultrasound should be performed in the emergency department. Early GI consultation should be pursued if clinical suspicion remains high despite reassuring laboratory or imaging studies, as many of the imaging modalities in the emergency department are poorly sensitive in detecting the disease. Diagnosis should then be confirmed using EUS, MRCP, or ERCP, the last of which can also be therapeutic.

References

1. Zackria R. Postcholecystectomy Syndrome. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK539902/. Published December 7, 2020. Accessed December 24, 2020.
2. Ahmed M. Acute cholangitis - an update. World Journal of Gastrointestinal Pathophysiology. 2018;9(1):1-7. doi:10.4291/wjgp.v9.i1.1
3. Chong VH, Chong CF. Biliary complications secondary to post-cholecystectomy clip migration: a review of 69 cases. J Gastrointest Surg. 2010 Apr;14(4):688-96. doi: 10.1007/s11605-009-1131-0. Epub 2010 Jan 5.
4. Rumsey S, Winders J, Maccormick AD. Diagnostic accuracy of Charcots triad: a systematic review. ANZ Journal of Surgery. 2017;87(4):232-238. doi:10.1111/ans.13907
5. Lee, D.-ho, Ahn, Y. J., Lee, H. W., Chung, J. K., and Jung, I. M. (2016). Prevalence and characteristics of clinically significant retained common bile duct stones after laparoscopic cholecystectomy for symptomatic cholelithiasis. Annals of Surgical Treatment and Research, 91(5), 239. https://doi.org/10.4174/astr.2016.91.5.239
6. Choi, Y.S., Do, J.H., Suh, S.W. et al. Risk factors for the late development of common bile duct stones after laparoscopic cholecystectomy. Surg Endosc 31, 4857–4862 (2017). https://doi-org.uc.idm.oclc.org/10.1007/s00464-017-5698-3
7. Georges N, Ford C, Moreno M, Zagroba S. Point-of-Care Ultrasound Assisting in the Rapid Diagnosis of Acute Cholangitis 60 Years After Cholecystectomy. J Emerg Med. 2022 Jan;62(1):e8-e10. doi: 10.1016/j.jemermed.2021.07.001. Epub 2021 Sep 9. PMID: 34511296.
8. Glaenzer B, Molvar C. Choledocholithiasis: Evaluation, Treatment, and Outcomes. Seminars in Interventional Radiology. 2016;33(04):268-276. doi:10.1055/s-0036-1592329
9. Tripathi N. Conjugated Hyperbilirubinemia. StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK562172/. Published August 25, 2020. Accessed December 22, 2020.
10. Foley WD, Quiroz FA. The Role of Sonography in Imaging of the Biliary Tract. Ultrasound Quarterly. 2007;23(2):123-135. doi:10.1097/01.ruq.0000263851.53549.a5
11. Cline D, Ma OJ, Meckler GD, et al. Tintinallis Emergency Medicine: a Comprehensive Study Guide. New York: McGraw-Hill Education; 2020.
12. Sugiyama M, Atomi Y. Endoscopic ultrasonography for diagnosing choledocholithiasis: a prospective comparative study with ultrasonography and computed tomography. Gastrointestinal Endoscopy. 1997;45(2):143-146. doi:10.1016/s0016-5107(97)70237-2
13. Spataro J, Tolaymat M, Kistler CA, Jacobs M, Fitch J, Ahmed M. Prevalence and Risk Factors for Choledocholithiasis After Cholecystectomy. American Journal of Gastroenterology. 2017;112. doi:10.14309/00000434-201710001-00072
14. Solomkin, J. S., Mazuski, J. E., Bradley, J. S., Rodvold, K. A., Goldstein, E. J. C., Baron, E. J., O'Neill, P. J., Chow, A. W., Dellinger, E.
15. Costi R, Gnocchi A, Di Mario F, Sarli L. Diagnosis and management of choledocholithiasis in the golden age of imaging, endoscopy and laparoscopy. World J Gastroenterol. 2014 Oct 7;20(37):13382-401. doi: 10.3748/wjg.v20.i37.13382. P., Eachempati, S. R., Gorbach, S., Hilfiker, M., May, A. K., Nathens, A. B., Sawyer, R. G., & Bartlett, J. G. (2010). Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clinical Infectious Diseases, 50(2), 133–164. https://doi.org/10.1086/649554
15. Costi R, Gnocchi A, Di Mario F, Sarli L. Diagnosis and management of choledocholithiasis in the golden age of imaging, endoscopy and laparoscopy. World J Gastroenterol. 2014 Oct 7;20(37):13382-401. doi: 10.3748/wjg.v20.i37.13382.

5-FU Toxicity

Continued from page 9

there appears to be limited evidence of the efficacy of pretreatment for or treatment of ischemic events associated with 5-FU with nitrates or calcium channel blockers. It is recommended that patients who have underlying cardiovascular disease, or who have cardiac symptoms associated with 5-FU use, undergo cardiac monitoring during medication administration or be transitioned to an alternative therapeutic regimen altogether.[25-27] Patients experiencing ischemic symptoms or demonstrating EKG changes associated with 5-FU administration should be evaluated as any other patient experiencing cardiovascular-related chest pain, including coronary angiography when indicated.

Summary

Chest pain in a cancer patient should prompt thorough evaluation on presentation, regardless of the quality or severity of pain. While pulmonary embolism and other common etiologies of chest pain should remain high on the differential, the case above highlights the importance of considering less frequently identified causes of chest pain to include chemotherapy-induced acute coronary vasospasm. If a provider suspects chemotherapy-induced pathology in the emergency department, even in the setting of a reassuring diagnostic workup, it may be reasonable to discuss disposition as well as further chemotherapeutic management with their primary oncologist prior to discharge.

References

1. Becker K, Erckenbrecht JF, Häussinger D, Fueling T. Cardiotoxicity of the antiprolif erative compound fluorouracil. Drugs. 1999;57(4):475-484.
2. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. Cardiology journal. 2012;19(5):453-457.
3. Wacker A, Lersch C, Scherpinski U, Reindl L, Seyfarth M. High incidence of angina pectoris in patients treated with 5-fluorouracil. Oncology. 2003;65(2):108-112.
4. Meydan N, Kundak I, Yavuzsen T, et al. Cardiotoxicity of de Gramont's regimen: incidence, clinical characteristics and long-term follow-up. Japanese journal of clinical oncology. 2005;35(5):265-270.
5. De Forni M, Malet-Martino MC, Jaillais P, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. Journal of Clinical Oncology. 1992;10(11):1795-1801.
6. Rezkalla S, Kloner RA, Ensley J, et al. Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. Journal of Clinical Oncology. 1989;7(4):509-514.
7. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiopathy. Cancer. 1993;71(2):493-509.
8. Talapatra K, Rajesh I, Rajesh B, Selvamani B, Subhashini J. Transient asymptomatic bradycardia in patients on infusional 5-fluorouracil. Journal of cancer research and therapeutics. 2007;3(3):169.
9. Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. Internal medicine journal. 2010;40(4):303-307.
10. Oztop I, Gencer M, Okan T, et al. Evaluation of cardiotoxicity of a combined bolus plus infusional 5-fluorouracil/folinic acid treatment by echocardiography, plasma troponin I level, QT interval and dispersion in patients with gastrointestinal system cancers. Japanese journal of clinical oncology. 2004;34(5):262-268.
11. Meyer CC, Calis KA, Burke LB, Walawander CA, Grasela TH. Symptomatic cardiotoxicity associated with 5-fluorouracil. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1997;17(4):729-736.
12. Jensen SA, Hasbak P, Mortensen J, Sørensen JB. Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. Journal of clinical oncology. 2010;28(36):5280-5286.
13. Çalık AN, Çeliker E, Velibey Y, Çağdaş M, Güzelburç Ö. Initial dose effect of 5-fluorouracil: rapidly improving severe, acute toxic myopericarditis. The American journal of emergency medicine. 2012;30(1):257. e1-257. e3.
14. Dalzell JR, Samuel LM. The spectrum of 5-fluorouracil cardiotoxicity. Anti-cancer drugs. 2009;20(1):79-80.
15. Cerny J, Hassan A, Smith C, Piperdi B. Coronary vasospasm with myocardial stunning in a patient with colon cancer receiving adjuvant chemotherapy with FOLFOX regimen. Clinical colorectal cancer. 2009;8(1):55-58.
16. Friedman MA, Sadée W. The fluoropyrimidines: biochemical mechanisms and design of clinical trials. Cancer chemotherapy and pharmacology. 1978;1(2):77-82.
17. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. Clinical pharmacokinetics. 1989;16(4):215-237.
18. Farina A, Malafronte C, Valsecchi MA, Achilli F. Capecitabine-induced cardiotoxicity: when to suspect? How to manage? A case report. Journal of Cardiovascular Medicine. 2009;10(9):722-726. doi:10.2459/JCM.0b013e32832bb9b1
19. Gorgulu ş, Seden C, Tuna T. A case of coronary spasm induced by 5-fluorouracil. Acta cardiologica. 2002;57(5):381-383.
20. Shoemaker LK, Arora U, Lima CMSR. 5-Fluorouracil–induced coronary vasospasm. Cancer Control. 2004;11(1):46-49.
21. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. Journal of cancer research and clinical oncology. 2008;134(1):75-82.
22. Labianca R, Beretta G, Clerici M, Fraschini P, Luporini G. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. Tumori Journal. 1982;68(6):505-510.
23. Luwaert R, Descamps O, Majois F, Chaudron J-M, Beauduin M. Coronary artery spasm induced by 5-fluorouracil. European heart journal. 1991;12(3):468-470.
24. Südhoff T, Enderle M-D, Pahlke M, et al. 5-Fluorouracil induces arterial vasocontractions. Annals of oncology. 2004;15(4):661-664.
25.Giza DE, Boccalandro F, Lopez-Mattei J, et al. Ischemic heart disease: special considerations in cardio-oncology. Current treatment options in cardiovascular medicine. 2017;19(5):37.
26. Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents. Drug safety. 2000;22(4):263-302.
27.Chong JH, Ghosh AK. Coronary artery vasospasm induced by 5-fluorouracil: proposed mechanisms, existing management options and future directions. Interventional Cardiology Review. 2019;14(2):89.
28. Senkus E, Jassem J. Cardiovascular effects of systemic cancer treatment. Cancer treatment reviews. 2011;37(4):300-311.
29.Mosseri M, Fingert HJ, Varticovski L, Chokshi S, Isner JM. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. Cancer research (Chicago, Ill). 1993;53(13):3028-3033.
30. Thyss A, Gaspard M, Marsault R, Milano G, Frelin C. Very high endothelin plasma levels in patients with 5-FU cardiotoxicity. Annals of oncology. 1992;3(1)
31. Levin ER. Endothelins. New England Journal of Medicine. 1995;333(6):356-363.
32. Perrino C, G Schiattarella G, Magliulo F, et al. Cardiac side effects of chemotherapy: state of art and strategies for a correct management. Current vascular pharmacology. 2014;12(1):106-116.
33. Patel B, Kloner RA, Ensley J, Al-Sarraf M, Kish J, Wynne J. 5-Fluorouracil cardiotoxicity: left ventricular dysfunction and effect of coronary vasodilators. The American journal of the medical sciences. 1987;294(4):238-243.

Human Trafficking

Continued from page 11

To learn more about human trafficking, scan the QR code below to read Dr. Kelli Jarrell's article from 2019 on Taming the SRU.[16]

References

1. Human Trafficking. United Nations Office on Drugs and Crime.
2. Tiller J, Reynolds S. Human Trafficking in the Emergency Department: Improving Our Response to a Vulnerable Population. West J Emerg Med. 2020;21(3):549-554. doi:10.5811/westjem.2020.1.41690
3. Global Estimates of Modern Slavery: Forced Labour and Forced Marriage. Int Labor Organ. Published online September 2017.
4. Shandro J, Chisolm-Straker M, Duber H, et al. Human Trafficking: A Guide to Identification and Approach for the Emergency Physician. Ann Emerg Med. Published online April 26, 2016.
5. Anderson V, Kulig T, Sullivan C. Estimating the Prevalence of Human Trafficking in Ohio: Executive Summary Report. Published online February 1, 2019.
6. Lederer L, Wetzel C. The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities. Ann Health Care Law. 23(1):61-91.
7. ACOG Committee. Caring for Patients Who Have Experienced Trauma: ACOG Committee Opinion Summary, Number 825. Obstet Gynecol. 2021;137(4):757–758. doi:10.1097/AOG.0000000000004328
8. SAMHSA's Concept of Trauma and Guidance for a Trauma-Informed Approach. Published online July 2014. 10.
9. What is Trauma-Informed Care? University and Buffalo. Published 2015. http://socialwork.buffalo.edu/social-research/institutes-centers/institute-on-trauma-and-trauma-informed-care/what-is-t16.rauma-informed-care.html
10. Ravi A, Little V. Providing Trauma-Informed Care. Am Fam Physician. 2017;95(10):655-657.
11. Anthony B. On-Ramps, Intersections, and Exit Routes: A Roadmap for Systems and Industries to Prevent and Disrupt Human Trafficking. Published online July 2018.
12. Curtis R, Terry K, Dank M, Dombrowski K, Khan B. Commercial Sexual Exploitation of Children in New York City. CSEC Popul N Y City Size Charact Needs. 2008;1.
13. Human Trafficking Prevention: Strategies for Runaway and Homless Youth. Published online November 2020.
14. Off The Streets. Cincinnati Union Bethel. Accessed March 10, 2022. https://cubcincy.org/how-we-help-2/off-the-streets/
15. Human Trafficking Initiative. Dave Yost Ohio Attorney General. https://www.ohioattorneygeneral.gov/humantrafficking
16. Jarrell K. Annals of B-Pod: Human Trafficking. Taming the SRU.

Annals of B Pod is always looking for interesting cases to publish! Please submit cases via EPIC In Basket message to Kristin Meigh. Make sure to include the providers involved in the case.

Submitted B Pod Cases

Case	Providers
Milk Alkali Syndrome	Gobble/Thode/Hill
Choledocholithiasis	Iparraguirre/Benoit
Human Trafficking	Jarrell/Mand
5-FU Toxicity	Ferreri/Goel
Hyperkalemia	Gawron/McDonough