Oral Vignette Session C

The Appropriate Use of Medical Futility in Treatment Decisions at the End of Life
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LEARNING OBJECTIVES: 1. Assess medical futility in relation to treatment goals near the end of life. 2. Recognize the ethical application of unilateral Do-Not-Resuscitate orders.

CASE INFORMATION: A 47-year-old female with metastatic colon cancer presented from home with fever, rigors and weakness. Her examination and work-up was consistent with cholangitis and treatment was initiated with antibiotics and placement of a percutaneous biliary drain. In spite of a short interval of improvement, the patient's hospital course was further complicated by bilateral hydronephrosis and acute renal failure secondary to tumor progression. Anuria and massive volume overload ensued and the patient developed hypoxic respiratory failure requiring intubation and transfer to the ICU. Sepsis was evolving secondary to fungemia and bladder invasion by the tumor necessitated frequent blood transfusions. The patient was unresponsive and unable to interact with her family or doctors. Given the patient's advanced disease and multi-organ system failure, the ICU team expressed to the family that in this tragic situation, future escalation of care would be medically futile. The family maintained that the patient had openly communicated her desire to pursue all life-sustaining therapy and to retain a full code status. A younger brother of the patient had a prolonged survival with lymphoma in the setting of aggressive therapies and the patient's own sister had survived ovarian cancer. The patient's family members were united in their view that the patient had wished to maintain life as long as possible, declaring that their faith has led them to hope for a miracle despite the grim prognosis given by the medical team. To withhold treatment was seen by the family as a betrayal of the promise they had made to respect her wishes. Despite the families' preferences for aggressive care, the ICU team decided that CPR was medically futile, and would only increase suffering without prolonging survival. The patient was administratively made DNR and eight days later she died. The local police were then contacted by family who believed the patient had suffered a wrongful death.

IMPLICATIONS/DISCUSSION: The concept of futility is often used to withhold or withdraw care from patients with advanced disease. Medical futility is defined as a clinical action that cannot achieve a stated goal for an individual patient. However, quantitative criteria by which futility can be measured do not exist. Futility is ultimately a value-based determination which cannot be made without first establishing concrete treatment goals. As highlighted in the above scenario, if the patient's goal is to maintain physiologic life, then CPR may not be a futile intervention.

A unilateral decision to withhold life-sustaining measures based on the principle of futility risks imposing religious or subjective values regarding the end-of-life onto patients and their families. Such actions may foster a culture of paternalism and present an opportunity for misuse as providers may try to avoid difficult discussions. Yet, to require that physicians deliver care believed to be ineffective or misguided poses a threat to one's professional integrity and violates the principle of first doing no harm. Medical futility should not be used as a justification for rejecting a patient or proxy's preferences, but can be used as a framework for discussing goals of care. A hierarchy in which physician autonomy should take precedence over patients' self-determination does not exist. When a resolution cannot be reached, hospital ethics teams should be consulted to facilitate mediation and to advocate for both patients and physicians. Ultimately, medical futility is not grounds for unilateral treatment decisions. Case law, state statutes, and professional codes of ethics will be used as examples to exhibit these points.
LEARNING OBJECTIVES: 1. Recognize the emerging phenomenon of opioid induced neurotoxicity in patients who are receiving opioids for cancer related pain. 2. Understand how to evaluate suspected opioid induced neurotoxicity, and how to manage patients with this disorder.

CASE INFORMATION: A 57 year old man with prostate cancer presented with low back pain. He was tender to palpation over the lower back and right femur but neurologically intact. Hydromorphone patient controlled analgesia (PCA) was started at a bolus dose of 0.4mg intravenously (IV) with a lockout of 10 minutes and no basal rate (0.4/10/0). MRI revealed diffuse bony metastases throughout the thoracic and lumbar spine and a pathologic right femoral neck fracture. PCA was titrated to 14/10/9 over the next 3 days. He underwent radiation to his spine and right total hip replacement with improvement in pain, but remained on the same PCA settings until 6 days later, when his PCA was titrated to 20/10/9 because of worsening pain. The following day, the patient complained of muscle spasms and confusion. On exam, he was alert but delirious, experiencing visual hallucinations and 16 beats of myoclonus per minute in his upper extremities. Basic chemistry panel and complete blood count were normal. A diagnosis of opioid induced neurotoxicity was made. PCA was stopped for 90 minutes, then restarted with a bolus only at 50% of prior dose and no basal dose (10/10/0). Lorazepam was scheduled for myoclonus. His symptoms resolved within 48 hours.

IMPLICATIONS/DISCUSSION: Ongoing clinician education has resulted in an appropriate increase in opioid use to manage cancer related pain and dyspnea. This changing pattern in opioid utilization has led to enhanced symptom control in cancer, but has also led to the emergence of opioid induced neurotoxicity. The incidence of opioid induced neurotoxicity is unknown. Neuroexcitatory effects of opioids may be seen in all patients on opioids, but comorbid conditions, including renal failure, can precipitate opioid induced neurotoxicity. Effects are likely caused by the 3-glucuronide opioid metabolites, which have no analgesic effect and can accumulate rapidly. Myoclonus is usually the presenting symptom of opioid induced neurotoxicity and if missed can progress to hyperalgesia, allodynia, delirium, and tonic-clonic seizures. If clinicians are unaware of opioid induced neurotoxicity, they may mistakenly treat hyperalgesia with higher opioid doses and facilitate the progression of opioid induced neurotoxicity. Evaluation includes blood work to look for renal dysfunction, physical exam to assess hydration status, and a thorough chart review of opioid dosages and dose changes. Clinical management entails treatment of exacerbating factors. If pain remains controlled, dose reduction of the opioid may be necessary along with initiation of a benzodiazepine to reduce myoclonus and raise the seizure threshold. If pain is uncontrolled, opioid rotation to a structurally dissimilar opioid at 25-50% of the morphine equianalgesic dose may be necessary. Naloxone does not treat opioid induced neurotoxicity, and should not be used.
**Metronidazole-Induced Encephalopathy** Maria Han 1; Cynthia Margaret Cooper1. 1Massachusetts General Hospital, Boston, Massachusetts. (Tracking ID # 11160)

**LEARNING OBJECTIVES:**
1. Identify the symptoms of metronidazole-induced encephalopathy, MIE
2. Recognize the characteristic findings of MIE on magnetic resonance imaging

**CASE INFORMATION:** Patient is a 64-year-old female who presented with dysarthria. Two months prior, she had an above-the-knee amputation. Three weeks prior, she developed diarrhea positive for C. difficile toxin and began an extended course of metronidazole. Days prior, she received doses of IV prochlorperazine for nausea. That day, she was discharged to rehab where her family found her confused and requested her return.

She complained her tongue felt too big for her mouth and of pain in her limbs. Speech was slow, hypophonic, and dysarthric. She had odd oral movements with frequent tongue thrusting. There was subtle arm weakness and diminished reflexes. Toxicology screen and cultures were negative. Brain MRI showed non-specific subcortical T2 FLAIR signal abnormalities.

Prochlorperazine-induced dyskinesia was suspected and this medication discontinued. Oral dyskinesia resolved but dysarthria and paresthesias persisted. She became lethargic and developed flaccid paresis.

Motor conduction study showed reduced signal amplitude and conduction. CSF had normal protein and no leukocytes. ABG demonstrated hypoxia and hypercarbia. She was intubated.

Repeat MRI showed symmetric T2 FLAIR signal hyperintensity of the subcortical white matter in the frontal and parietal lobes, corpus callosum, midbrain red nuclei, and dentate nuclei. Findings were felt to be consistent with metronidazole-induced encephalopathy, MIE.

Metronidazole was discontinued, after a cumulative dose of 65g. Ataxia improved though weakness persisted. Subsequent MRI showed less hyperintensity in the midbrain and dentate nuclei. Polyneuropathy only minimally improved with IV immunoglobulin.

**IMPLICATIONS/DISCUSSION:** Metronidazole is widely used for the treatment of anaerobic, abdominal and genitourinary infections, including C. difficile colitis. Common side effects include nausea and altered taste. Neurologic side effects are uncommon and include seizures and peripheral neuropathy. MIE is a rare complication with less than 20 previous case reports.

MIE typically manifests as cerebellar dysfunction, including ataxia and dysarthria. Symptoms have been reported with cumulative doses ranging from 25g to 1080g. Symptoms usually resolve within 7 days of discontinuation.

The characteristic MRI finding is bilateral symmetric T2 hyperintense lesions of the dentate nuclei. Lesions may affect the brainstem, corpus callosum, and subcortical white matter. The differential includes other toxic or viral leukoencephalitides and Marchiafava-Bignami Disease. Radiographic improvement typically begins within 14 days of antibiotic cessation.

Neurotoxicity has been attributed to drug binding of ribonucleic acid and inhibited protein synthesis. Axonal edema may produce the characteristic MRI findings. Why certain brain areas are preferentially affected in MIE remains unclear.

MIE should be considered in any patient receiving a high cumulative dose of metronidazole who presents with new-onset cerebellar dysfunction.
Crack You Once, Crack You Twice: Recurrent Agranulocytosis Associated With Repeated Levamisole Contaminated Cocaine
Jonathan D Kirsch

LEARNING OBJECTIVES: 1. Recognize an adverse effect of cocaine contaminated with levamisole 2. Consider levamisole contaminated cocaine in the differential diagnosis of unexplained agranulocytosis

CASE INFORMATION: A 51 year old female with a history of acute hepatitis B, gluten intolerance and intermittent cocaine abuse presented to the emergency department with a swollen, painful, red fifth digit on her right hand consistent with cellulitis. Her absolute neutrophil count (ANC) was 0.1 x 10^9/L. She admitted to recent, intermittent cocaine abuse. Her medications included prn acetaminophen. She is allergic to sulfa. Her past medical history was otherwise unremarkable.

Her hospital course included an extensive hematologic, infectious, and rheumatologic workup. Guided by a recent MMWR report [12/18/09 58(49)] highlighting an unexplained etiology of agranulocytosis, levamisole contamination of cocaine was considered, but not checked at that time. Her urine toxicology screen was positive for cocaine. Her lab workup also showed an elevated anti-SSA antibody and ANA of 1: 640, but was otherwise unremarkable. A skin biopsy of her necrotic finger lesion was consistent with neutrophilic dermatosis thought to be Sweet's syndrome without vasculitis. The patient was treated with filgastrim (G-CSF) until her neutropenia resolved and she was discharged with antibiotics for cellulitis that resolved as an outpatient. She was counseled on cocaine cessation and was set up with outpatient resources.

She returned twice over the subsequent 6 months with similar presentations: periorbital cellulitis with neutropenia and 1st digit cellulitis with neutropenia. Her ANC was 0.5 and 0.6 x10^9/L, respectively. On both of these latter occasions, she had a positive urine toxicology for cocaine and her urine levamisole level was elevated. Both hospitalizations were uncomplicated, being treated with G-CSF on the second admission and spontaneously recovering on the final admission. She did not follow up for repeat hematologic or rheumotologic workup.

IMPLICATIONS/DISCUSSION: Neutropenia is a rare event (7.2 cases per 1,000,000 population per year) in patients not receiving cytotoxic drugs. While technically agranulocytosis refers to ANC less than 0.1 and neutropenia is less than 0.5, the terms are often used synonymously in the literature. Levamisole has been used to cut cocaine since at least 2005, presumably due to its similar appearance and texture to cocaine, low cost, and availability for use in veterinary medicine as an anti-helminthic agent on livestock farms. Levamisole now contaminates up to 90% of cocaine confiscated in the U.S., though its domestic availability is limited due to decreased production and restricted use to treating helmithic infections in goats. Case series suggest that women with rheumatologic disorders and HLA-B27 are more commonly affected though the etiology is unknown.

Agranulocytosis has been seen in up to 13% of individuals being treated with levamisole for rheumatoid arthritis and in breast cancer treatment. It is unknown what proportion of cocaine users exposed to levamisole are affected as most don't present for medical care and agranulocytosis is not a reportable event. Cocaine itself has not been associated with neutropenia. Clinicians should be suspicious of levamisole contaminated cocaine in patients presenting with unexplained neutropenia. Workup includes a urine toxicology screen, CBC with differential and urine or serum levamisole levels measured within 48 hours of drug use. There is no established treatment, as most cases resolve spontaneously. Close monitoring, consideration of treatment with G-CSF, and substance abuse counseling is recommended. The CDC is now performing national surveillance in some states.
LEARNING OBJECTIVES: 1. Recognize that ritonavir can increase the risk of iatrogenic Cushing’s syndrome in patients on inhaled corticosteroids. 2. Explore a type of systems error that can cause iatrogenesis.

CASE INFORMATION: The patient is a 48-year-old man with HIV (last CD4 count= 207, viral load

IMPLICATIONS/DISCUSSION: Inhaled corticosteroids are absorbed through both the lung and gastrointestinal tract. Fluticasone is a potent inhaled corticosteroid metabolized by P450 CYP3A4 and has been shown to suppress the hypothalamic-pituitary axis. Itraconazole and ritonavir, two inhibitors of CYP3A4, have been implicated in iatrogenic Cushing’s syndrome and/or adrenal insufficiency by decreasing inhaled corticosteroid metabolism in case reports. There are even some more recent case reports implicating intra-articular and epidural steroids in iatrogenic Cushing’s syndrome in patients on ritonavir. The diagnosis of ritonavir and fluorinated corticosteroid inhaler associated Cushing’s syndrome has been delayed in some cases due to attribution of weight gain to lipodystrophy from ART. In this case, though the primary care provider was aware of a potential drug interaction and attempted to discontinue the fluticasone, a pharmacy error led to its continued dispensation. The frequent usage of fluticasone in this patient led to a marked iatrogenic Cushing’s syndrome and adrenal insufficiency. Health care providers should be aware of the increased risk of drug interactions in patients on ritonavir given its potent inhibition of CYP3A4. This case also serves as a reminder to maintain a low threshold to directly verify medications with a pharmacy to ensure accuracy and safety. Systems errors such as dispensation of discontinued medications and erroneous instructions can occur despite attention by both health care providers and pharmacists.