A success among failures: Ceftaroline salvage therapy in complicated methicillin-resistant staphylococcus aureus (MRSA) bacteremia

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Learning Objective 1: Recognize the causes and potential solutions for first-line antibiotic failure in patients with MRSA bacteremia.

Case: A 29-year-old previously healthy Hispanic male was admitted with a 6-day history of fevers, chills, shortness of breath and left arm cellulitis. He was involved in a scuffle with the police about a week prior. On presentation, he had severe sepsis with acute kidney injury and pulmonary septic emboli. He was started empirically on vancomycin and piperacillin/tazobactam. His blood cultures grew MRSA with a vancomycin minimal inhibitory concentration (MIC) of 1. His condition worsened with higher fevers and WBC counts. He also developed cutaneous pustules that grew MRSA with vancomycin MIC of 2. His antibiotics were changed to daptomycin and clindamycin with no improvement. Fevers peaked at 101.5° F with a WBC count of 32,000/µL. CT scan of the chest without contrast showed cavitary changes in some of the septic emboli and new areas of consolidation. CT of left arm and abdomen showed no abscesses. Follow up blood cultures and transesophageal echocardiogram were negative. His antibiotics were changed to ceftaroline with gradual improvement, and he finished a 6-week course without side effects.

Discussion: MRSA continues to cause a significant morbidity and mortality. Despite better understanding of its resistance patterns and newly developed antibiotics, it continues to pose a formidable therapeutic challenge. Vancomycin and daptomycin are first line antibiotics for treating MRSA bacteremia. Vancomycin is reasonably well tolerated and is inexpensive. MRSA with MIC ≤ 2 is considered susceptible to vancomycin but clinical failure has been reported in MRSA infections with MIC between 1 and 2. This results from the low probability of current dosage regimens achieving the appropriate vancomycin concentration exposure (AUC/MIC ≥ 400). Daptomycin, on the other hand, is expensive, not suitable to treat pneumonias, and resistance to it has already been reported. Ceftaroline is a novel cephalosporin that has high affinity to penicillin binding protein 2a, a MRSA specific penicillin binding protein, which correlates with its efficacy against this pathogen. It is bactericidal and demonstrates time-dependent killing. It is currently approved for treating community-acquired pneumonia and skin and soft tissue infections. Clinical data to support its use in MRSA bacteremia is limited but in a rabbit endocarditis model it compared favorably to other antibiotics. Further studies to investigate its use in MRSA bacteremia are warranted.
Acute ischemic myocardial injury following administration of Definity contrast in a patient without coronary artery disease

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**Learning Objective 1:** Report an undocumented adverse event following administration of the Definity echocardiography contrast agent

**Case:** A 57 year-old white female with a history of postpartum cardiomyopathy diagnosed 11 years prior presented to the emergency department with progressive exertional dyspnea, orthopnea, and peripheral edema for the previous few days. She had neither seen a cardiologist nor had symptoms for many years. The patient was admitted with a diagnosis of acute congestive heart failure and her symptoms resolved quickly with diuretic therapy.

Physical examination was only remarkable for trace peripheral edema.

Other than a very mildly elevated brain natriuretic peptide (BNP) at 158 pg/ml, her initial laboratory tests including 3 sets of cardiac enzymes were within normal limits. Electrocardiogram (EKG) showed normal sinus rhythm with a previously documented left bundle branch block. Chest x-ray revealed cardiomegaly with pulmonary congestion. An echocardiogram was ordered to evaluate her heart failure, and Definity was used during the study to improve the diagnostic yield due to her large body habitus.

Immediately after Definity injection, the patient started having a burning sensation at the site of the injection followed by burning in the chest and shortness of breath. She was able to complete the test, but the pain intensified and was severe before subsiding after approximately 30 minutes. ECG at the time of the event did not reveal any ischemic changes, but troponin I rose to peak at 10.68 ng/ml 6 hours later. The echocardiogram showed a left ventricular ejection fraction of 35%, grade II diastolic dysfunction, and moderate mitral regurgitation. Cardiac catheterization done the following morning was negative for coronary artery disease (CAD). She was observed throughout the day without further incident and was discharged to follow up with her cardiologist.

**Discussion:** Definity is a contrast agent used to improve the diagnostic yield of echocardiography. The agent has survived a battery of clinical investigations after the Food and Drug Administration (FDA) placed a black box warning on the label, declaring it contraindicated for patients with cardiopulmonary disease such as myocardial infarction and pulmonary hypertension. The FDA subsequently recalled the contraindications after further exploration yielded a favorable risk-safety profile. Studies continue to be published that demonstrate the safety and utility of the agent. In the articles reviewed, we did not identify any cases of Definity-related acute coronary syndrome or myocardial injury in a patient without CAD. The immediacy of the reaction and lack of catheterization findings support our theory that the Definity-induced vasospasm was significant enough to cause myocardial injury. Although Definity is a crucial tool for the evaluation of patients with functional heart disease, it is important to recognize and anticipate occasional adverse reactions. Other serious reactions include anaphylactoid reactions, respiratory distress, and cardiac arrhythmias. We are reporting this case of probable Definity-induced vasospasm as an adverse event so that other clinicians are aware and prepared for such events. We support the continued observation of the FDA’s recommendation for a 30-minute monitoring period after administration of the agent.
Learning Objective 1: Recognize hypercalcemia secondary to Mycobacterium Avium Intracellulare (MAI) infection as a cause of altered mental status in a patient with acquired immune deficiency syndrome (AIDS)

Learning Objective 2: Explain the pathophysiology of hypercalcemia induced by granulomatous disease

Case: A 50-year-old man with acquired immune deficiency syndrome presented with abdominal pain for two weeks and increasing weakness, lethargy, and hallucinations for one week. He was non-adherent to antiretroviral therapy and his most recent cluster of differentiation 4 count was 8. He was agitated and having visual and auditory hallucinations; talking to people not in the room. There was no fever and no neck stiffness. His abdomen was soft, but the liver was enlarged with right upper quadrant tenderness. Pertinent laboratory findings include: white blood cell count 9.8 K/ul, alkaline phosphatase 418 U/L, corrected calcium 13.6 mg/dL, intact parathyroid hormone (PTH) 1.7 pg/mL (normal >10), 25-hydroxyvitamin D (calcidiol) 16 ng/mL (normal >30), 1,25 dihydroxyvitamin D (calcitriol) 45 pg/mL (normal 20-70), angiotensin-converting enzyme-level 73 U/L (normal <50). His head computed tomography scan and subsequent lumbar puncture were entirely unremarkable. Abdominal ultrasound revealed a 22 centimeter liver with increased echogenicity, typical of parenchymal disease. His liver biopsy revealed nonnecrotizing granulomas mainly centered on portal tracts with numerous acid fast bacilli (AFB) seen on staining. Subsequent AFB blood cultures confirmed disseminated Mycobacterium Avium Complex infection. This patient’s symptoms were thought to be a result of hypercalcemia caused by this granulomatous disease, and rapidly resolved with fluid hydration and MAI treatment.

Discussion: Altered mental status in the context of AIDS is often seen by physicians, but hypercalcemia is an uncommon etiology for such presentations. Hypercalcemia can also result in lethargy, weakness, myalgias, nausea, constipation, and abdominal pain. While often caused by primary hyperparathyroidism or malignancy in general populations, hypercalcemia is also seen in association with granulomatous diseases such as sarcoidosis, fungal infections, berylliosis, Crohn’s disease, tuberculosis, and other mycobacterial infections. The uncommon infectious causes of hypercalcemia are particularly important to consider in immunocompromised patients.

The mechanism by which granuloma formation causes hypercalcemia is via elevated levels of calcitriol. Usually, the conversion of calcidiol to calcitriol occurs in the proximal tubules of the kidneys via a 1-alpha-hydroxylase that is regulated by PTH, phosphorus, and calcium levels. Normally, hypercalcemia suppresses the release of PTH and thereby calcitriol production. In granulomatous disease there is excessive direct production of calcitriol by macrophages from calcidiol independent of PTH. It is thought that macrophages activate extra renal 1-alpha-hydroxylase leading to calcitriol mediated, PTH independent hypercalcemia. Our patient had low PTH and calcidiol levels, but disproportionately high calcitriol levels, supporting that his hypercalcemia was a manifestation of granulomatous disease. While the definitive treatment of hypercalcemia relies on treating the underlying etiology, bisphosphonates and glucocorticoids can also play a therapeutic role.
An Unusual Case of Chest Pain: Pericarditis Secondary to Hydralazine-Induced Lupus

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Learning Objective 1: Recognize clinical manifestations of drug-induced lupus

Learning Objective 2: Diagnose drug-induced lupus

Case: A 60-year-old male with hypertension, hyperlipidemia, diabetes, and coronary disease presented to the emergency department reporting a two-day history of intermittent chest pain with exertion, followed by an episode of chest pain at rest. He denied associated symptoms. His electrocardiogram was unchanged, and cardiac enzymes were negative. He was admitted for a stress test, which was negative for ischemia. During the admission, he developed fevers, leukopenia, transaminitis, arthritis, and new onset atrial fibrillation. His exam was notable for a pericardial friction rub and pulsus paradoxus of 12. Echocardiogram revealed a moderate pericardial effusion with evidence of elevated intra-pericardial pressure, and he underwent pericardiocentesis. Diagnostic work-up revealed a positive antinuclear antibody (ANA) with a 1:160 titer. Anti-dsDNA antibody was negative, but anti-histone antibody was positive. He had been on hydralazine for 1.5 years, and was diagnosed with hydralazine-induced lupus. Hydralazine was discontinued, he was started on prednisone and hydroxychloroquine, and he has since fully recovered.

Discussion: More than 80 medications have been identified as causes of drug-induced lupus (DIL). Procainamide, hydralazine, and quinidine are most commonly implicated; other medications include minocycline and anti-TNF alpha therapy. Unlike idiopathic systemic lupus erythematosus (SLE), which usually affects females ages 20-40, DIL affects men and women equally, with the average age of onset around 50. Clinical manifestations vary based on the inciting agent, and range from limited cutaneous involvement to systemic symptoms including fever, myalgias, arthralgias, arthritis, hepatosplenomegaly, and serositis. Hematologic abnormalities, renal disease, and neurologic disease are less common. Symptoms are generally milder than with SLE, but some cases are life threatening. Typical symptoms of hydralazine-induced lupus include fever, rash, arthralgias, myalgias, pleuritis, and leukopenia (1). Pericarditis is less common, occurring in <5% of cases (2). Approximately 95% of patients with DIL have a positive ANA, and >90% have anti-histone antibodies. Anti-dsDNA antibodies are rare. When a patient taking one of the implicated medications presents with the above symptoms, DIL should be suspected. However, confirming the diagnosis can be difficult, as there are no formal diagnostic criteria for DIL. A proposed set of criteria includes sufficient and continuing exposure to a specific medication, at least one symptom compatible with SLE, no previous history of SLE, and resolution of symptoms within weeks to months after discontinuation of the medication (2). The presence of anti-histone antibodies in the absence of anti-dsDNA antibodies strongly suggests DIL, but is not an official criterion for diagnosis (2). ANA positivity is also not a requirement for diagnosis. In general, DIL is a reversible condition with a favorable prognosis, but it is critical to diagnose early. Treatment involves cessation of the medication and supportive care. NSAIDs and anti-malarial agents may be used for musculoskeletal symptoms, and severe cases may benefit from treatment with corticosteroids. If symptoms do not resolve after stopping the medication, other diagnoses should be considered.1. Chang C, et al. Drug Saf 2011; 34(5):357-374.2. Borchers AT, et al. Ann NY Acad Sci 2007; 1108:166.
Weil’s Disease (Icteric Leptospirosis) Contracted on a Caribbean Cruise

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Learning Objective 1: Recognize the clinical presentation of leptospirosis

Learning Objective 2: Understand the diagnosis and treatment of leptospirosis

Case: A 54 year old man presented with worsening lower extremity pain, headache and fever for 4 days. The patient had no significant past medical history. Fourteen days prior to admission, while on a Caribbean cruise, he suffered a superficial abrasion on his left leg on a rainforest hike. Four days prior to admission he noted a severe, retro-orbital headache, chills, and fever up to 103°F. The fever dissipated after three days, followed by the onset of intense, bilateral thigh pain. Patient came to the hospital because of inability to walk due to severe muscle pain.

On physical exam his vital signs were significant for tachycardia. He had severe lower extremity weakness. Lung exam was clear to auscultation bilaterally. Abdominal exam was not significant.

A complete blood count revealed a white blood cell count of 10,000 k/mm², a hemoglobin of 14 g/dl and platelets of 45,000 k/mm². AST and ALT were 130 IU/L and 80IU/L, total bilirubin 2mg/dl and a creatine kinase of 8,000 U/L. A chest x-ray revealed mild interstitial infiltrates.

The patient became jaundiced with total bilirubin peaking at 45.8 mg/dL, and AST of 432 IU/L. He became anemic and required two units of packed red blood cells. Thrombocytopenia persisted. Worsening renal function and hypotension improved with aggressive intravenous hydration.

Initial tests were negative for viral hepatitis, HIV, Lyme disease, West Nile virus, Legionella, dengue virus, and leptospirosis. He was treated with intravenous penicillin for leptospirosis and azithromycin for disseminated legionella. One week later, repeat testing for Leptospira antibodies returned positive at a concentration of 1:400. He was discharged home on oral penicillin.

Discussion: Leptospirosis, caused by the spirochete Leptospira, is the most common zoonotic infection worldwide. It is transmitted through contact with urine from infected animals or contaminated fresh water. The prevalence in developing countries has spread, especially with the rising popularity of adventure tourism.

Leptospirosis should be considered in any traveler who returns from an endemic region with any combination of fever, retro-orbital headache, severe myalgias, photophobia, and vomiting. The incubation period ranges from ten days to three weeks. Infection is usually self-limited, however 5-10% of cases will progress to Weil’s disease (icteric leptospirosis). This is manifested by jaundice, acute renal failure, and hemorrhage. Pulmonary involvement, thrombocytopenia, and rhabdomyolysis may occur.

Distinguishing between Weil’s Syndrome and Dengue hemorrhagic fever can be challenging. Our patient’s laboratory values and presentation had features that were classic for both diseases. Thrombocytopenia, bilateral interstitial infiltrates and increased liver enzymes are more consistent with Dengue hemorrhagic fever. However, patients with Weil’s syndrome can have significant thrombocytopenia and develop liver failure with hyperbilirubinemia.

Diagnosis of leptospirosis is made with the microscopic agglutination test. It can take up to four weeks for this result to become positive and so initial titers may be negative. Standard treatment is penicillin or doxycycline.