To Friends of the Department of Medicine:

Earlier this academic year, The Institute of Medicine (IOM) issued their most recent report, “Resident Duty Hours: Enhancing Sleep, Supervision, and Safety,” which recommends changes to medical residents’ duty hours and workloads to “promote conditions for safe medical care, improve the education of doctors in training, and increase the safety of residents and the general public.” While the IOM simply makes recommendations, the Accreditation Council for Graduate Medical Education (ACGME) makes the actual rules that a residency program must follow in order to maintain accreditation. Under the leadership of the ACGME, one of the Residency Review Committees (RRC) establishes these accreditation guidelines for internal medicine residency programs. In March 2009, the ACGME will convene a duty hour conference to review the recent IOM report and discuss possible changes in current RRC rules. I will be attending this conference.

The IOM report recommends that the maximum residents’ work hours per week remain at 80 hours. However, the report diverges from the current duty hour limits by proposing a maximum shift length without protected sleep time of 16 hours. Specifically, the maximum shift length can be 30 hours provided there is a “5-hour uninterrupted continuous sleep period” between 10:00 p.m. and 8:00 a.m. The “16 hour rule” will be the main area of focus and contention as academic medicine comes to grips with the new challenges proposed by the IOM.

I believe a resident still can learn without 30 hour shifts. Moreover, we might find that residents read more when traditional overnight calls are eliminated. Ongoing studies investigating the best ways to learn in the complex healthcare system are essential to building better training programs.

Where do I stand on the new proposal? Currently, more than half of our teams already work 16 hour shifts, so this is not hard to accomplish. Furthermore, the safety imperative is not just for patients but also for our residents. First, we should not allow fatigued residents to enter orders after 24 hours of continuous duty—studies have shown that fatigue impairs human performance. But just as important, we should not allow fatigued residents to drive home after an extended shift.

The time for 16 hours is now!

I believe a resident still can learn without 30 hour shifts. Moreover, we might find that residents read more when traditional overnight calls are eliminated. Ongoing studies investigating the best ways to learn in the complex healthcare system are essential to building better training programs.

This debate promises to be interesting. I hope to contribute by reminding our leading educational bodies that safety is about the patient and the resident.

Gregory C. Kane MD, FACP, FCCP
Professor of Medicine
Residency Program Director
Vice-Chairman for Education
Department of Medicine
Jefferson Medical College

From the Desk of the Residency Program Director

Argentina, California, Kenya, Alaska — these are just a few of the places visited by our internal medicine residents and captured in breathtaking photographs that are exhibited throughout this issue of The Jefferson Medicine Forum. It is easy to appreciate the beauty of nature when taking in these pictures of stunning aerial views and colorful landscapes. Their display in this journal is fitting amongst the academic articles that speak to the intellectual curiosity of our residents and the diversity of pathology seen at Thomas Jefferson University Hospital.

The research and review articles in this journal highlight a commitment to evidence-based medicine and scientific inquiry. The art and poetry showcase talent and curiosity beyond the field of medicine and an appreciation for travel, humor, and humanity. Each case report reveals a fascinating clinical challenge. It is remarkable to consider that these cases represent only a fraction of the experiences in patient care and variety of pathology that our residents are exposed to everyday.

From the Editors

This issue of The Forum marks the 10th anniversary of this scholarly publication written and edited by the internal medicine residents. Like the photographs of diverse scenes in the United States and abroad, the case reports, review and research articles, poetry, and art within this journal reflect the breadth of interests and talents of our residents and their continual commitment to learning.

Senior Editors: Tamara Solitro, MD
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Ankitkumar Patel, MD
Anastasia Shnitser, MD

Editorial Staff: Andrew Foy, MD
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# Table of Contents

## Review Articles

**Congestive Heart Failure and Vitamin D Deficiency**  
Ankitkumar K. Patel, MD, MPH, Matthew DeCaro, MD, and Paul J. Mather, MD ........................................ 1

**Understanding Hyperparathyroidism in Renal Disease**  
Rosemary Nwoko, MD, and Kara Chenitz, MD ........................................................................ 3

**The Use Of Statins In Liver Disease: Risk Versus Benefit**  
Dina Halegoua-De Marzio, MD ........................................................................ 5

## Research Articles

**Tjuh Adherence to IDSA Guidelines for the Treatment of Cryptococcal Meningitis**  
Matthew Grant, MD ......................................................................................... 7

**Embracing Quality Improvement at Resident Clinic: a Report Card on Our Diabetes Care**  
Tamara Solitro, MD ......................................................................................... 9

## Case Reports

**A 68 Year-old Woman With Leukemia Under Her Skin**  
Ben Creelan, MD, Hari Nair, MSIII, and Joanne Filicko-O’Hara, MD ........................................ 12

**A 31 Year-old Man With Chest Pain, Rash, and EKG Changes**  
Neerav Sheth, MD, Rahul Anand, MD, and Matthew Stopper, MD ........................................ 14

**A Man With Invasive Community Acquired-MRSA Infection in the ICU Setting**  
Jason Korenblit, MD, MBA ........................................................................ 17

**Severe Heart Failure and Large Left Ventricular Thrombus Following Acute Myocardial Infarction**  
Ankitkumar K. Patel MD, MPH, Scott Silvestry, MD, and Paul J. Mather, MD ......................... 21

**Jaundice in a Leukemia Patient Status-Post Allogeneic Stem Cell Transplantation**  
Esther Lee, MD .......................................................................................... 23

**A 57 Year-old Man With Prolonged Shortness of Breath and Fevers**  
Loren Chen, MD .......................................................................................... 25

**A 61 Year-old Man With Delayed Hypersensitivity Reaction to Joint Prosthesis**  
Regina C. Lee, MD ..................................................................................... 29

**Primary Care Follow Up Post Mitral Valve Surgery at Ambulatory Clinic**  
Andrew Yin, MD ..................................................................................... 31

**A 55 Year-old Man With Mental Status Change and Severe Anemia**  
Sujeet Jagpal, MD, and Anastasia Shnitser, MD ........................................ 34

**A College Student with Fulminant Hepatic Failure**  
Christie Crawford, MD ............................................................................... 35
A CASE OF DRUG-INDUCED HEPATOTOXICITY: AMIODARONE IS NOT ALWAYS TO BLAME
Brendan O’Hare, MD...................................................................................................................................................... 37

A WOMAN WITH CHEST PAIN, SYCNOPE, AND TRANSAMINITIS
Ankitkumar K. Patel, MD, MPH, and Brendan O’Hare, MD............................................................................................ 40

VITAMINS: FRIEND OR FOE
Anastasia Shnitser, MD, and Dina Halegoua-De Marzio, MD......................................................................................... 44

A CASE OF SEVERE ANEMIA IN AN AIDS PATIENT
Amy K. Slenker, MD, and Rahul Anand, MD.................................................................................................................. 45

MAN WITH SWOLLEN EYE, BLURRED VISION, AND FEVERS IN THE SETTING OF NEWLY DIAGNOSED MDS
Rory Bowers, MD............................................................................................................................................................. 47

A TALE OF TWO WOMEN: IS THERE A BENEFIT TO BILEVEL VENTILATION IN PREGNANCY?
Laura Immordino, MD, and Adam Kaufman, MD............................................................................................................ 51

A WOMAN WITH MASSIVE SPLENOMEGALY
Erin Meschter, MSIII, Michelle Choi, MD, and Lisa Teng, MD.............................................................................................. 54

A CASE OF DIABETIC MUSCLE INFARCTION DESPITE GOOD DIABETIC CONTROL
Tessey Jose, MD, and Intekhab Ahmed, MD....................................................................................................................... 57

ELDERLY MAN WITH WEIGHT LOSS, WEAKNESS, AND ANOREXIA
Austin Hwang, MD.......................................................................................................................................................... 59

HEMOPHTYSIS AS A PRESENTING SYMPTOM FOR METASTATIC PANCREATIC CANCER
Toshimasa Okabe, MD, Leigh Van Vranken, MSIII, and Darren N. Seril, MD ............................................................... 61

CLINICAL IMAGES
CLINICAL IMAGE: LARGE FUNGUS BALL AND PULMONARY EMBOLUS
Matthew Grant, MD ....................................................................................................................................................... 65

CLINICAL IMAGE: COLORECTAL FOREIGN BODY
Stephen Koczirka, MSIV, Anastasia Shnitser, MD, and Dina Halegoua-De Marzio, MD ................................................. 66

POETRY
PAINLESS JAUNDICE
Nilay Kavathia, MD ....................................................................................................................................................... 67
**Congestive Heart Failure and Vitamin D Deficiency**

*Ankitkumar K. Patel, MD, MPH, Matthew DeCaro, MD, and Paul J. Mather, MD*

**Introduction**

Congestive heart failure (CHF) is a chronic medical condition whose incidence is rising. The prevalence of CHF is approximately 1% to 3% in Western countries. Despite innovations in medical therapy, CHF is associated with high morbidity and mortality rates. CHF patients commonly experience muscle weakness and fatigue as two major symptoms. An altered intracellular handling of ionized calcium has been suggested to play a vital role in impaired myocardial contraction. In isolated myocytes from patients with end stage heart failure, systolic ionized calcium levels were markedly decreased, while diastolic levels were elevated as compared to healthy controls. In addition, digitalis and beta-blocker medical therapy is frequently used in CHF patients and is known to increase myocardial ionized calcium levels.

**Vitamin D Sources and Action**

Solar ultraviolet B radiation penetrates the skin and converts 7-dehydrocholesterol to previtamin D3 which is then converted to vitamin D3. Vitamin D3 is then metabolized in the liver to 25-OH vitamin D. This is often used to determine a patient’s vitamin D status. 25-OH vitamin D is converted in the kidneys to its active form 1,25-OH vitamin D, and this conversion is regulated by parathyroid hormone levels, serum calcium and phosphorus levels.

People get vitamin D from sunlight exposure, diet, and dietary supplementation. Only a few foods such as eel, herring, and salmon are good sources of vitamin D. Fortunately, ultraviolet B-induced synthesis of vitamin D is extremely effective. More than 200 genes, which regulate cellular proliferation, differentiation, apoptosis, and angiogenesis, are either directly or indirectly controlled by 1,25-OH vitamin D. It is also associated with increased insulin production, decreased renin synthesis and increased myocardial contraction.

Receptors for the vitamin D hormone (VDR) exist in a variety of cell types including osteoblasts, myocytes, cardiomyocytes, pancreatic cells, endothelial cells, neurons, and immune cells. In vitro studies demonstrate that vitamin D suppresses pro-inflammatory cytokines (e.g., IL-6, IL-2, interferon-gamma, TNF-alpha) and upregulates levels of the anti-inflammatory cytokine (e.g., IL-10).

**Epidemiology of Vitamin D Deficiency**

The different stages of vitamin D status can be classified as deficiency, insufficiency, hypovitaminosis, adequacy and toxicity. Vitamin D deficiency is associated with severe clinical symptoms such as rickets, osteomalacia, myopathy, and calcium malabsorption. In vitamin D insufficiency biochemical alterations such as mild hyperparathyroidism and low intestinal calcium absorption are noted without severe clinical symptoms. In addition, calcitriol levels remain normal at the expense of elevated parathyroid hormone. In hypovitaminosis D, the body stores of vitamin D are already low but only minor physiological abnormalities, such as an elevated PTH level are seen. In vitamin D adequacy there are no disturbances in dependent bodily functions. Finally, in vitamin D toxicity there is intestinal calcium hyperabsorption and increased bone resorption which leads to hypercalcemia.

In the National Health and Nutrition Examination Survey (NHANES III), low 25-OH vitamin D levels were associated with multiple medical problems including coronary vascular disease, cancer, congestive heart failure, hypertension and diabetes. Although there is no consensus, many researchers believe an optimal level of 25-OH vitamin D to be 30ng/mL or more. With this number, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency. Unfortunately, 41% of men and 53% of women in the United States (U.S.) have levels of 25-OH vitamin D below 28ng/mL. In the elderly population in the U.S. and Europe that are still living in the community (not in nursing homes) 40% to 100% are vitamin D deficient.

Risk factors for developing vitamin D deficiency include sunscreen usage, dark skin, breast fed infants, aging, inflammatory bowel disease, fat malabsorption disease, obesity and a sedentary lifestyle. Severe deficiency often develops in completely immobile patients. Interestingly, one study found that 93% of people presenting to an emergency department with complaints of muscle aches and bone pain and who had a vast array of medical diagnoses were deficient in vitamin D. Circulating levels of 25-OH vitamin D depend largely on exposure to ultraviolet B light. Serum 25-OH vitamin D levels decrease with age because of the diminishing capability of the skin to produce previtamin D.

**Vitamin D Deficiency and CHF**

In many patients CHF is the end stage of hypertensive, coronary, and valvular cardiovascular disease. There is increasing evidence to support the notion that low vitamin D status may be an important factor in the development and pathogenesis of CHF. Patients with CHF have reduced circulating levels of 25-OH vitamin D and calcitriol and increased levels of serum phosphorus and PTH. In an observational study, patients with severe CHF were found to have vitamin D deficiency as well as hyperparathyroidism. Excess PTH levels increase blood pressure and cardiac contractility and lead to hypertrophy of cardiac myocytes and interstitial fibrosis. Serum 25-OH vitamin D is a major factor in determining the plasma level of PTH in normal and CHF patients.

In addition, cardiac muscle cells have a vitamin D receptor and a calcitriol-dependent ionized calcium binding protein. In experimental vitamin D deficiency models, calcitriol adminis-
tration can normalize impaired myocardial contractility. Calcitriol is also known to be a negative endocrine regulator of the renin-angiotensin-aldosterone system (RAAS), which when inappropriately stimulated results in hypertension. A case report demonstrated that intravenous calcitriol treatment decreased the plasma activity of renin and angiotensin II, lowered blood pressure and reversed myocardial hypertrophy. In one study of hypertensive patients, who were exposed to ultraviolet B radiation three times a week for three months had a 180% increase in 1,25-OH vitamin D and both systolic and diastolic blood pressure reduced by 6mmHg.

CHF patients have been shown to have significantly lower 25-OH vitamin D levels during the winter months (November-April) than during the summer months (May-October) which are results similar to healthy controls. However, CHF patients have low outdoor activity due to disease symptoms and thus have limited opportunity to generate adequate previtamin D from the skin. This limitation may potentiate or worsen their clinical condition during the winter months.

Interestingly, Zittermann et al report data in an unpublished case control study that suggests that lifestyle factors that influence vitamin D differ during childhood, adolescence and adulthood in CHF patients versus controls. This data suggests that patients have a low vitamin D status in these ages even when they are free from CHF.

The Future
As the incidence of congestive heart failure increases in the U.S. population, a greater focus will be needed to better elucidate the role of Vitamin D in the pathogenesis of symptoms. Further research, in the form of randomized controlled trials is necessary to determine whether Vitamin D supplementation can reduce the progression of heart failure. In the near future it is important to determine whether Vitamin D can be used as a marker of disease progression.

References
UNDERSTANDING HYPERPARATHYROIDISM IN RENAL DISEASE
Rosemary Nwoko, MD, and Kara Chenitz, MD

The parathyroid glands are four pea-sized glands located on the four corners of the thyroid gland. They secrete parathyroid hormone (PTH), which maintains calcium and phosphorus homeostasis. PTH regulates calcium such that when serum levels of calcium fall too low, it increases the serum calcium level by stimulating more calcium release from the bones, increasing intestinal absorption of calcium and decreasing calcium excretion into the urine. When the serum calcium normalizes, the parathyroid gland shuts off the production of PTH. An excess of PTH in the system throws off the calcium-phosphorus homeostatic balance, resulting in various symptoms and clinical effects.

Hyperparathyroidism can be of two types: primary and secondary. The former is commonly due to an adenoma or hyperplasia of one or more of the four glands. In rare cases, primary hyperparathyroidism can be secondary to a malignancy in the glands. Secondary hyperparathyroidism occurs when elevated PTH levels are caused by pre-existing medical conditions such as calcium malabsorption syndromes, disorders of vitamin D and phosphate metabolism, dietary calcium deficiency or any other pre-existing condition that causes low serum calcium levels with a resultant compensatory increase in PTH levels. Chronic renal failure is the most common cause of secondary hyperparathyroidism and will be the focus of this review. CKD patients have high phosphate and low calcium levels causing hypocalcemia and a resultant stimulation of the parathyroid glands.

Patients with hyperparathyroidism develop a wide array of symptoms and complications, although some patients may be asymptomatic initially. This includes but is not limited to myopathy, fatigue, pruritis, abdominal pain, renal calculi, confusion, memory problems, osteoporosis, and increased thirst and urination (due to the increased excretion of calcium into the urine causing an osmotic effect). With continued elevation of PTH and therefore serum calcium levels, conjunctival, corneal, vascular and cutaneous calcification can occur with severe consequences. Vascular calcification is the most dreaded complication of hyperparathyroidism because it results in plaque accumulation that increases the risk of cardiovascular death. Patients can develop calcium calcification in the myocardium, coronary arteries, and cardiac valves. They are also at risk for palpitations, hypertension, and arrhythmias such as atrial fibrillation. Indeed, the most common cause of death in end stage renal disease (ESRD) patients is cardiovascular disease. As another example of a serious complication, cutaneous calcification can result in ulceration and gangrene. Hyperparathyroid induced bone disease, or osteitis fibrosa cystica, which is due to increased osteoclast and osteoblast activity, also occurs commonly with longstanding hyperparathyroidism.

Medical management of hyperparathyroidism includes calcium supplements, vitamin D analogs, phosphate binders and/or calcimimetics that have various mechanisms of action to suppress the high PTH level. Calcium stimulates the G-protein linked calcium sensing receptor (CaSR), inhibiting the release of PTH at secondary sites (e.g., c cells of thyroid gland, kidney cells, osteoblasts, GI mucosa, and hematopoietic cells in the bone marrow). Vitamin D acts directly on parathyroid cell vitamin D receptors to inhibit PTH release and phosphate binders work by binding phosphate in the intestinal lumen. Calcimimetics, such as cinacalcet, increase the CaSR’s sensitivity to serum calcium. Calcimimetics are especially beneficial because they stimulate the calcium receptors without additionally increasing calcium, unlike vitamin D analogs. Also this class of drugs is particularly useful in those patients with ESRD who have nodular hyperplasia of the parathyroid gland which causes decreased expression of extracellular CaSR and even greater reduction in vitamin D receptor density. This leads to decreased efficacy of calcium and vitamin D analogs. When medical therapy fails, surgical removal by subtotal parathyroidectomy is the next available option.

At this point, there is no official standard of care regarding the absolute indications for parathyroidectomy in hyperparathyroidism generally or with respect to patients with ESRD. Many of the symptoms discussed earlier can be present in dialysis patients who do not have markedly elevated levels of PTH, who therefore would not benefit from parathyroidectomy. As mentioned above, a nodular, hyperplastic parathyroid gland provides fewer options for medical treatment, so in these cases surgery may be indicated. In renal transplant recipients, most hyperparathyroidism improves post transplantation but when it does not, the persistent hyperparathyroidism may adversely affect renal function, leading to consideration of surgical intervention. Studies have shown that parathyroidectomy has beneficial effects on humoral immunological markers. The effects are thought to be due to the marked PTH reduction and partly improved nutritional state after surgery. Though this may be an attractive postoperative benefit, no studies have suggested that this is an indication for surgery. Unfortunately, post-transplant parathyroidectomy itself has been shown to be associated with abrupt decompensation of renal allografts, so if patients have persistent hyperparathyroidism despite renal transplantation and medical therapy, they are left with grim options; they can either continue medical therapy and risk calciphylaxis, or get surgery and risk graft failure. Overall, since most abnormal parathyroid function normalizes after transplantation, there is little evidence to suggest a prophylactic parathyroidectomy is efficacious in patients on the renal transplant list. For now, nephrologists must rely on clinical instinct for the management of hyperparathyroidism, while research is underway delineating particular standards of care in this area.
References

Photograph courtesy of Anastasia Shnitser, MD
The Use Of Statins In Liver Disease: Risk Versus Benefit
Dina Halegoua-De Marzio, MD

Introduction
The National Cholesterol Education Program periodically produces Adult Treatment Panel (ATP) updates as warranted by current clinical scientific research in cholesterol management. Each of the guideline reports, ATP I, II, and III, has a major role in guiding physicians how to treat abnormal cholesterol levels. Recent clinical trials demonstrate that LDL-lowering therapy with statins (HMG-CoA inhibitors) reduces total mortality, coronary mortality, major coronary events, coronary procedures and strokes in patients with established coronary heart disease. However, the ATP III has cited active or chronic liver disease as an absolute contraindication to the use of statins. The reason for this contraindication goes back to the initial clinical trials of Lipitor (atorvastatin), which demonstrated that persistent elevations (> 3 times the upper limit of normal) in serum transaminases occurred in 0.7% of patients who received atorvastatin. The incidence of these abnormalities was 0.2%, 0.2%, 0.6% and 2.3% for 10, 20, 40 and 80 mg atorvastatin, respectively. Based on this information, the recommendation held that liver function tests should be performed before the initiation of treatment with statins, following each dosage increase, and periodically thereafter.

Although several reports of significant liver injury associated with statins have appeared in the literature, in reality it occurs rarely. Current labeling of statins is ambiguous; for example, what exactly does active liver disease or persistent unexplained liver function tests (LFTs) elevations mean? Also there is an assumption that acute hepatotoxicity that develops in a patient with impaired liver function would potentially be more fatal, although evidence-based data to support this theory are lacking. The fact remains that statins are the most efficacious drugs for decreasing low-density lipoprotein cholesterol levels, and cardiovascular disease is the leading cause of mortality in the United States. Thus, it is important to establish whether statin therapy should be withheld from patients with liver disease.

Risk of Statin Hepatotoxicity
The following question must be addressed: are patients with elevated liver enzymes at a higher risk for statin hepatotoxicity? Chalasani et al and Vuppalanchi et al evaluated the affect of starting statin therapy on the LFTs among patients with baseline normal LFTs and those with baseline abnormal LFTs. They determined that patients with baseline LFT elevation had a greater incidence of a mild to moderate increase in LFTs during treatment as compared to those without baseline LFT abnormalities. The study also compared patients on statin therapy with baseline elevated LFTs to patients with elevated baseline LFTs and no history of statin use. The study showed elevations in LFTs regardless of statin use. Therefore, the study surmised that elevations in LFTs in patients with baseline abnormalities while using statins may be due to underlying liver disease and not statin use.

One of the most common causes of undiagnosed abnormal LFTs is nonalcoholic steatohepatitis (NASH). NASH is characterized by steatosis, inflammation and occasionally fibrosis of the liver that can progress to cirrhosis. Rallidis et al studied the safety and efficacy of pravastatin treatment on histological markers of disease activity in patients with NASH. The study suggested a possible beneficial role of statins in the treatment of NASH and showed that the patients with NASH were not at an increased risk of LFT abnormalities secondary to statin use. This clarification is important because many patients with NASH are at a higher risk for cardiac events due to common co-morbidities such as metabolic syndrome, hypercholesterolemia, obesity and diabetes.

In clinical practice, the treatment of hyperlipidemia may necessitate an increase in statin dosage to achieve the target goals recommended by the ATP III. This leads to increased concerns about statin-induced hepatotoxicity in patients with chronic liver disease who require high doses of statin. This concern stems from older clinical trials which showed an increased risk of LFT elevations in patients taking high dose statins. A recent study by Lewis et al compared pravastatin 80 mg to a placebo in a double-blind clinical trial. The medications were administered daily to hypercholesterolemic subjects greater than 18 years of age with at least a six-month history of compensated chronic liver disease and a low-density lipoprotein cholesterol (LDL-C) level greater than or equal to 100 mg/dL. In comparison to placebo, high-dose pravastatin (80 mg/day) significantly lowered LDL, total cholesterol, and triglycerides and was safe and well tolerated.

Recent research also contests the need for routine transaminase screening in patients taking statins. In a study by Smith et al, 1002 patients on statins were tested, and 10 (1%) of the patients were identified as having significant LFT elevations while 5 (0.5%) patients were identified as having moderate LFT elevations. None of the elevations appeared to be directly related to statin use, and no adverse outcomes were related to these abnormal lab values. Therefore, the risk of severe transaminase elevations with statin use is low. In addition, routine transaminase monitoring may be unnecessary since it has low yield and excessive cost. The monitoring may also lead to unnecessary evaluation of slightly abnormal laboratory findings as well as the discontinuation of a highly effective medication.

The Liver Expert Panel and Final Conclusions
The National Lipid Association (NLA) is a nonprofit, multidisciplinary medical society focused on enhancing the practice of lipid management in clinical medicine. The Task Force, created in June of 2005, was a two-year independent NLA initiative to extensively review and evaluate the safety of statins and other lipid-modifying drugs. After compilation of the analysis and commissioned research, these experts presented their conclusions to four Expert Panels who reviewed and considered
the evidence relative to their respective fields of expertise: nephrology, hepatology and neurology.

The Liver Expert Panel published their findings in the American Journal of Cardiology in 2006. The panel’s key message was that there is no proof that statins cause life-threatening liver damage. LFT elevations are usually reversible after stopping the statin therapy and do not cause long-term damage. Routine liver enzyme monitoring is not needed during statin therapy. If an isolated asymptomatic transaminase level of one to three times the upper limits of normal is detected, the statin does not need to be discontinued. If the transaminase level is more than three times the upper limits of normal during routine evaluation, the test should be repeated; if it is still elevated, further evaluation should be pursued. Although routine transaminase monitoring in patients taking statins is unnecessary, clinicians should be alert to patient reports of jaundice, malaise, fatigue and other possible signs of hepatotoxicity. If there is an objective evidence of significant liver injury, the statin should be discontinued. In conclusion, statin therapy can be safely administered to patients with chronic liver disease, compensated cirrhosis, and NASH.

References
TJUH Adherence to IDSA Guidelines for the Treatment of Cryptococcal Meningitis
Matthew Grant, MD

Introduction
Cryptococcal meningitis is an infectious complication of immune compromised states that carries a high rate of mortality or relapse. Although Infectious Disease Society of America (IDSA) guidelines outline the recommended treatment regimen for cryptococcal meningitis, clinicians take a heterogenous clinical approach. This study examines the use of antifungal regimens in treating cryptococcal meningitis at a tertiary care hospital.

Objectives
The primary endpoint was to determine the percentage of patients who received antifungal treatment that was backed by the highest Sobel class recommendation (i.e., “A1”) from the most recent IDSA-endorsed guidelines. Secondary endpoints were mortality and clinical relapse.

Methods
After review of TJUH fungal culture data from 2003 to 2007, this study included patients who had either:

1. A positive cerebrospinal fluid culture (CSF) for C. neoformans (12 patients)
2. A positive blood culture with signs/symptoms of meningitis (1 patient)

After appropriate patients were identified, chart reviews were performed to obtain pertinent demographic, laboratory and treatment data (see Table 1). Treatment strategies were then compared to the most recent IDSA-endorsed practice guidelines.

For HIV+ patients, the class A1 recommendation for the treatment of cryptococcal meningitis involves all of the following:

1. “Induction” – 2 weeks of amphotericin B (0.7-1 mg/kg/d) + flucytosine (100mg/kg/d in divided doses), followed by
2. “Consolidation” – 10 weeks of fluconazole 400 mg/d, followed by
3. “Maintenance” – lifelong fluconazole at 200 to 400 mg/d

For HIV negative patients, two endorsed regimens exist. The first is identical to that for HIV+ patients except maintenance therapy is not needed, and the second regimen is simply extended induction therapy for six to ten weeks without either consolidation or maintenance.

Results
Of the eleven HIV+ patients identified with cryptococcal meningitis, two (18%) were treated with a regimen consistent with the IDSA-endorsed class A1 recommendations. Of the two

| Table 1. Patient baseline characteristics at presentation. |
|---------------------------------|-----------------|
| Patient Characteristics | 1st presentation |
| Age, Years [Median (Min, Max)] | 42 (37, 58) |
| Sex - Male | 12 |
| Ethnicity | |
| Caucasian | 1 |
| African-American | 12 |
| Recent Antifungal Therapy | 0 |
| Comorbidities | |
| Diabetes Mellitus | 1 |
| Corticosteroid Therapy | 0 |
| Concurrent Bacterial Infection | 3 |
| HIV seropositive | 11 |
| CD4+ count [Median (Min, Max)] | 14 (2, 155) |
| Viral load [Median (Min, Max)] | 146,642 (<75, >750,000) |
| HAART | 2 |
| Pneumocystis jiroveci prophylaxis | 1 |
| MAI prophylaxis | 1 |
| Concurrent cryptococcal fungemia | 7 |
| CSF | |
| WBC count [Median (Min, Max)] | 32 (1, 635) |
| Protein [Median (Min, Max)] | 101 (41,855) |
| Glucose [Median (Min, Max)] | 40 (4, 63) |

HIV negative patients with cryptococcal meningitis, one was treated with an endorsed regimen (see Table 2).

For the HIV + subset, the most common deviations from the guidelines were as follows (note multiple deviations were present in some patients):

1) Flucytosine use during induction
   a. Failure to use – 4 patients
   b. Insufficient duration – 4 patients
   c. Insufficient dose – 1 patient
2) Insufficient duration of amphotericin B – 2 patients
3) Insufficient duration of fluconazole during consolidation – 2 patients
For the secondary endpoint analysis, all five observed instances of death or clinical relapse were in patients who had non-endorsed induction regimens (see Table 2).

### Table 2. Clinical outcomes by treatment categories.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th># of pts with relapse or death /# of pts treated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV (+) patients</strong></td>
<td></td>
</tr>
<tr>
<td>Induction therapy</td>
<td></td>
</tr>
<tr>
<td>Appropriate Regimen</td>
<td>0 / 3</td>
</tr>
<tr>
<td>Inappropriate Regimen</td>
<td>5 / 8</td>
</tr>
<tr>
<td>Consolidation therapy</td>
<td></td>
</tr>
<tr>
<td>Appropriate Regimen</td>
<td>0 / 2</td>
</tr>
<tr>
<td>Appropriate After Inappropriate Induction</td>
<td>4 / 7</td>
</tr>
<tr>
<td>Inappropriate Regimen</td>
<td>1 / 2</td>
</tr>
<tr>
<td><strong>HIV (-) patients</strong></td>
<td></td>
</tr>
<tr>
<td>Induction therapy</td>
<td></td>
</tr>
<tr>
<td>Appropriate Regimen</td>
<td>1 / 1</td>
</tr>
<tr>
<td>Inappropriate Regimen</td>
<td>1 / 1</td>
</tr>
</tbody>
</table>

### Conclusion

The vast majority of patients diagnosed at TJUH with cryptococcal meningitis from 2003 to 2007 were not treated with the IDSA-endorsed regimen. Despite a small sample size, a significantly lower rate of mortality and relapse was seen in patients who received the IDSA-endorsed regimen.

Practitioner barriers to guideline adherence need to be further studied, and likely involve fear of antifungal side effects, logistical complexity of the overall treatment regimen and the belief that amphotericin B monotherapy during induction is non-inferior. With specific regard to the lack of clinician adherence to flucytosine recommendations, it is worthwhile to note that no outcome-based study exists that directly compares amphotericin B monotherapy (at currently recommended doses) to flucytosine combination therapy; the current recommendation to use combination therapy is based on a high quality study that demonstrated more rapid CSF sterilization. Perhaps completion of such a randomized trial that demonstrates improved clinical outcomes with flucytosine addition would change future clinical practice.

### References

Embracing Quality Improvement at Resident Clinic: A Report Card on Our Diabetes Care
Tamara Solitro, MD

Background
The age of embracing the status quo or the “if it ain’t broke, don’t fix it” philosophy in medical practice is long gone. The goal of quality improvement in the medical field is one we can all appreciate: to optimize the delivery of health care and use advanced knowledge and technology to improve patient care. Many industries, such as automobile and engineering, already apply the scientific method to quality improvement efforts, and the time has come for medical practices to follow suit.

The Improvement Guide: A Practical Approach to Enhancing Organizational Performance1 describes a model of improvement that can be used in a variety of settings, including medical practices. Their model is based on cycles of “trial-and-learning,” emphasizing the importance of testing change on a small scale and observing its effects.

The “PDSA Cycle” provides a practical and systematic framework for making improvements in the workplace which epitomizes this “trial-and-learning” philosophy. The acronym PDSA stands for Plan, Do, Study, Act. The “Plan” phase involves stating the objective of the test and outlining the details of its execution. The plan is executed during the “Do” phase. Analyzing and summarizing the data occurs during the “Study” phase. Finally, the “Act” phase involves determining further changes that will make up the next cycle.

As quality improvement becomes an increasingly significant part of practicing medicine, there is much we can learn from its principles and applications during residency training. Jefferson Hospital Ambulatory Practice (JHAP), an outpatient clinic where internal medicine residents provide ambulatory care to a largely underserved population, presents an ideal setting for evaluating our own competence and quality of care.

Methods
To evaluate physician performance in practice as a component for certification, the American Board of Internal Medicine (ABIM) developed Web-based self-assessment programs for physicians called “practice improvement modules” (PIMs).2 The ABIM Diabetes PIM, for example, uses information collected from medical record audits to gauge performance rates for evidence-based measures of diabetes care, such as hemoglobin A1c levels. Voluntary patient surveys about diabetes care at the clinic are also scored. The ABIM Internet-based program then presents a summary report of the practice’s performance, allowing the physician(s) to view areas for improvement and develop a quality improvement plan.

Applying the ABIM Diabetes PIM at JHAP produced a report card of our diabetes care that highlights several opportunities for improvement and characterizes our patient population. Thirty medical records of diabetic patients who have been at JHAP for at least one year and seen in the last 12 months were randomly audited for review, and 17 patient surveys were completed.

Results and Discussion
Patient characteristics are reviewed in Table 1. The sample of patients are 50 years old on average, mostly female gender (73%), of black or African-American race (67%), and have had type 2 diabetes for greater than one year (80%).

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black or African-American</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Type of Diabetes</td>
</tr>
<tr>
<td>Type 1, &lt; 12 months</td>
</tr>
<tr>
<td>Type 1, &gt; 12 months</td>
</tr>
<tr>
<td>Type 2, &lt; 12 months</td>
</tr>
<tr>
<td>Type 2, &gt; 12 months</td>
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</tbody>
</table>

Target medical goals and patient evaluations show room for improvement. Table 2 illustrates the rates of diagnostic testing and complete patient evaluation. The majority of patients are appropriately tested for hemoglobin A1c and cholesterol levels, but less than 50% are tested for the presence of protein in the urine. Patient evaluations are mostly complete, but few diabetic patients undergo foot and eye exams. Table 3 demonstrates that less than half of
diabetic JHAP patients reach target goals for blood pressure, cholesterol, and hemoglobin A1c levels.

### Table 2. Diagnostic Testing and Patient Evaluation

<table>
<thead>
<tr>
<th>Diagnostic Testing</th>
<th>Percentage completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C tested w/in 12 months</td>
<td>87%</td>
</tr>
<tr>
<td>LDL cholesterol tested w/in 12 months</td>
<td>77%</td>
</tr>
<tr>
<td>HDL cholesterol tested w/in 12 months</td>
<td>77%</td>
</tr>
<tr>
<td>Triglycerides tested w/in 12 months</td>
<td>77%</td>
</tr>
<tr>
<td>Test for urine protein tested w/in 12 months</td>
<td>48%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Evaluation</th>
<th>Percentage completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>88%</td>
</tr>
<tr>
<td>Height</td>
<td>77%</td>
</tr>
<tr>
<td>Weight</td>
<td>97%</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>100%</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>100%</td>
</tr>
<tr>
<td>Foot exam</td>
<td>17%</td>
</tr>
<tr>
<td>Eye exam</td>
<td>27%</td>
</tr>
</tbody>
</table>

### Table 3. Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure &lt; 130/80</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>LDL cholesterol &lt; 70 in patients with CVD</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>LDL cholesterol &lt; 100 mg/dL; tested w/in 12 months</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>HDL cholesterol &gt; 40 mg/dL; tested w/in 12 months</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Triglycerides &lt; 150 mg/dL; tested w/in 12 months</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>HbA1C &lt; 7.0%, tested w/in 12 months</td>
<td>8 (27%)</td>
</tr>
</tbody>
</table>

### Table 4. Treatment and Preventative Care

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eligible</th>
<th>Treatment Prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individualized medical nutrition therapy</td>
<td>30</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Individualized physical activity plan</td>
<td>30</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Other treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>9</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Statin or other lipid-lowering drug</td>
<td>23</td>
<td>13 (57%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>30</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Smoking cessation support</td>
<td>7</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Antihyperglycemic Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single oral anti-hyperglycemic agent</td>
<td>30</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Combination oral anti-hyperglycemic agents</td>
<td>30</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Insulin</td>
<td>30</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Preventative Care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza vaccine during most recent flu season</td>
<td>30</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>30</td>
<td>3 (10%)</td>
</tr>
</tbody>
</table>

ABIM’s Diabetes PIM also reports data on our treatment plans for diabetic patients (Table 4). Smoking cessation support is highly successful. However, most patients require an individualized nutrition and exercise plan. The lower rates for prescribing medications such as aspirin, ACE inhibitors or angiotensin receptor blockers (ARBs), and statins point out potential areas for improvement. Similarly, our rates for influenza and pneumococcal vaccines are low and deserve attention.

The patient surveys provide useful information about patient satisfaction and opportunities for health education. Overall diabetic patients report a positive experience at JHAP. A majority (82%) of patients say they would recommend the practice to others. Most patients felt the practice managed their blood pressure, cholesterol, and blood sugars well, but many wanted more education about nutrition, their medications, and foot care. Also only 53% report taking aspirin regularly. These surveys thus underscore specific areas for improving patient education and compliance.

Knowledge of our performance rates in diabetes care may increase awareness of these opportunities for improvement among internal medicine residents and change patient care for the better. An intervention is currently in progress which aims specifically to improve our rates of pneumococcal vaccinations amongst diabetic patients at JHAP. Later, we will analyze whether the intervention effectively improved preventative care for our patients.

Like many ambulatory clinics serving a mostly underserved community, JHAP faces challenges to optimal medical care including variable patient education and adherence. Nonetheless, this self-assessment and future quality improvement endeavors can hopefully motivate us to address potential weaknesses, learn
about quality improvement in medical practice, and continue to
strive towards the highest standards of patient care.

Acknowledgements
Resident participants Kartik Patel, MD, Matthew McClure, MD,
and Talya Spivack, MD; Faculty advisors Mark Graham, MD, and
John Caruso, MD; and ABIM mentor Eric Holmboe, MD.

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Photograph courtesy of Anastasia Shnitser, MD
A 68 YEAR-OLD WOMAN WITH LEUKEMIA UNDER HER SKIN

Ben Creelan, MD, Hari Nair, MSIII, and Joanne Filicko-O’Hara, MD

Introduction
A wide spectrum of skin manifestations occurs in leukemia. Skin lesions are often due to infection, drug reaction, or inflammation.1 Rarely, extramedullary leukemia can invade the skin and is called leukemia cutis.2 Leukemia cutis is the infiltration of neoplastic leukocytes into the dermis or subcutaneous tissue, resulting in an identifiable skin lesion. These lesions show a varied morphology, and confirmatory immunohistochemical stains are needed for the diagnosis. Leukemia cutis may occur before, after, or concomitantly with the onset of systemic leukemia.3 Here we report a case of leukemia cutis occurring simultaneously with newly diagnosed acute myelogenous leukemia.

Case Report
A 68 year-old Caucasian female presented with a dry cough and malaise for two weeks. She noted fever as high as 101°F for the past two days. The patient reported visiting her primary care physician the previous week for routine lab work. She was contacted by her primary doctor and told to go to the ER because of decreased platelets and increased white blood cells. The patient did not take any medications. Past medical history was significant for spinal surgery in 1996 and 2001, which was complicated by superficial bacterial infection. She had never smoked, used alcohol or illicit substances. Allergy and family history was noncontributory.

Figure 2. Dermal biopsy of the skin lesion demonstrates infiltrating atypical cells (image A) expressing myeloperoxidase and focally CD38 (image B).

Physical exam was significant for a papule on the right cheek. This erythematous, firm papule had well-defined borders measuring approximately 3 x 2 cm above the nasolabial fold on the right cheek (Figure 1). The patient attributed this to mosquito bites during a recent weekend camping trip. Laboratory testing revealed leukocytosis (30 x 109/l), anemia (7.3 g/dL) and
thrombocytopenia (50 x 109/l). Manual differentiation revealed 31% blast cells. Bone marrow biopsy revealed acute myelogenous leukemia with multilineage dysplasia (AML, FAB M4). A single punch skin biopsy to a depth of 40 millimeters was performed. The biopsy showed dermal infiltrates of atypical cells expressing myeloperoxidase and focally CD38 (Figure 2). A c-kit stain revealed infiltration of mast cells consistent with leukemia cutis. The patient was treated with induction cytarabine and idarubicin, and her leukemia cutis lesion resolved within one week of initiation of chemotherapy. Her day #14 and day #30 bone marrow biopsies revealed no residual neoplastic disease.

**Discussion**

Patients with AML generally present with vague complaints related to complications of pancytopenia including weakness and easy fatigue. Skin findings in AML commonly include pallor, petechiae, or ecchymoses. Leukemic involvement of the skin is uncommon. When present, it is most often found in patients with monocytic or myelomonocytic AML variants. The overall incidence of leukemia cutis in AML is unclear but varies from 3% to 13% in separate case series. About 23% to 44% of leukemia cutis is diagnosed at the same time as the systemic malignancy, as in our case. Less than 10% are discovered before systemic disease can be identified, and the remainder of cases appears afterwards. The frequency of leukemia cutis is much higher in children with congenital leukemia; in fact as many as 25% to 30% of infants develop cutaneous involvement. In contrast to adult disease, this does not confer a worse prognosis.

Leukemia cutis is due to the local proliferation of leukemic cells into the dermis, epidermis, and subcutaneous tissue. The underlying molecular basis for the migration of leukemic cells to the skin is still unclear. It is hypothesized that the two ligands, Thymus Activation-Regulated Chemokine (TARC/CCL17) and Macrophage-Derived Chemokine (MDC/CCL22) are expressed on the skin, which attract adult T-cell leukemic cells to the skin. T-cell related antigens are also present on the cell surface of leukemic cells in acute monocytic leukemia (AML-M5), which may promote selective tropism of these cells to the skin surface. Additional studies have shown Cutaneous Lymphocyte-associated Antigen (CLA) staining in 78% of patients with myelomonocytic leukemia cutis patients, suggesting that CLA may play a role in leukemic invasion of the skin.

The classic lesions of leukemia cutis are red-brown to violaceous-plum papules or plaques of varying sizes. The legs are involved most commonly, followed by arms, back, chest, scalp and face. Due to the varied clinical presentation, a biopsy of the lesion with immunohistochemical studies is often necessary. Histological findings of leukemia cutis typically show a diffuse infiltration of leukemic cells in the dermis and subcutaneous tissue, often squeezed between collagen bundles. Involvement of blood vessels and skin adnexa are seen in the granulocytic, monocytic and myelomonocytic variants of leukemia cutis.

The development of leukemia cutis portends a poor prognosis in adults. More than 90% of these patients will have other sites of extramedullary involvement, and in 40% of these cases, the meninges will be involved. The disease course is usually aggressive, and length of survival is short. Studies have shown that the average survival time in AML patients with leukemia cutis is 7.5 months, and the overall survival rate is 6% at 2 years compared to 30% in AML patients without leukemia cutis. Even with this poor prognosis, long-term disease-free survival is possible with curative therapy directed at the skin, bone marrow and other sites of extramedullary involvement.

**References**

A 31 Year-old Man With Chest Pain, Rash, and EKG Changes

Neerav Sheth, MD, Rahul Anand, MD, and Matthew Stopper, MD

Case Presentation

A 31 year-old Caucasian male with no significant past medical history presents with increasing dizziness, chest pain, and shortness of breath of one day duration. On returning from a camping trip to Northern Pennsylvania three weeks prior to admission, he noted high fevers, “joint pains all over,” and a pink blotchy rash all over his chest and back. He did not recall any insect, tick or animal bites. His primary physician, who clinically suspected Lyme disease, ordered Lyme serologies and offered a prescription for doxycycline which the patient declined. Two weeks later, the patient presented to the emergency department after the onset of chest pain that he described as sharp, radiating to both arms, occurring with exertion and relieved by rest. The chest pain was associated with worsening shortness of breath and dizziness.

The patient denied taking any medications, herbal or other supplements. He admitted to smoking half a pack of cigarettes per day, drinking 20 alcoholic beverages per week and occasionally smoking marijuana. He denied any intravenous drug use. He also denied any recent travel outside the United States or exposures to new chemicals or pets. The patient’s mother had leukemia; his father had hypertension, diabetes, and hyperlipidemia; and his brother died from an anaphylactic reaction to shellfish.

On physical exam, the patient had a temperature of 99.6° Fahrenheit, heart rate of 50 beats/minute, blood pressure of 155/77 mm Hg, respiratory rate of 14 breaths/minute with an oxygen saturation of 100% on room air. The exam also revealed a regularly irregular rhythm with no murmurs, rubs or gallops. His lungs were clear to auscultation bilaterally. He had no focal neurological deficits nor was he orthostatic. Large, well demarcated macular erythematous lesions were noted on his back and thorax. Initial labs showed a white blood cell count of 10,000 cells/mm3 with a normal differential, normal serum chemistries, and a negative troponin. Peripheral smear was negative for babesiosis. The patient’s admission chest radiograph showed clear lungs without evidence of infiltrate or effusion. His initial EKG (Figure 1) showed a sinus rhythm at an atrial rate of approximately 100 beats/minute and a high-grade atrioventricular (AV) block with a variable ventricular response of about 40 beats/minute. The patient was admitted to telemetry, and a transcutaneous pacer was placed. Empiric intravenous ceftriaxone was begun to treat for a clinical diagnosis of Lyme carditis.

Figure 1. The patient’s admission EKG showed high grade AV block with variable conduction.
Lyme IgM and IgG antibody titers were positive, but Lyme PCR was negative. A transthoracic echocardiogram revealed mild mitral regurgitation, normal left ventricular size and thickness with hyperdynamic function. His ejection fraction was approximately 85%. By day two of hospitalization, his EKG had changed to sinus rhythm and second degree AV Block with 2:1 conduction (Figure 2). He was treated with intravenous ceftriaxone for 28 days with follow up in the cardiologic clinic two weeks after discharge. The repeat EKG at the follow up visit showed a return to normal sinus rhythm (Figure 3).

Discussion
Lyme disease is a multi-system spirochetal infection caused by Borrelia burgdorferi affecting up to 20,000 Americans each year. A Diagnosis of Lyme disease requires a high index of suspicion and a good history. The majority of patients will report travel to an endemic region, but many will not recall a tick bite.1,2,3 Upon exposure, patients enter an asymptomatic incubation phase (lasting from three to 32 days). This phase is identified only by a localized skin reaction at the site of inoculation that is secondary to spirochetal infiltration of the dermis and epidermis.3 Following this, patient presentation varies depending on the phase of the disease. Table 1 depicts the symptoms associated with subsequent phases of Lyme disease if left untreated.

Our patient’s symptomatology places him in the “Early Disseminated Phase,” presenting with fluctuating AV block ranging from first degree heart block to high grade AV dissociation with variable conduction. Cardiovascular complications may occur in up to 8% of patients with untreated Lyme disease.10 AV block is the most common cardiovascular manifestation of Lyme disease, attributed to spirochetal infiltration of the conduction system.4 AV block secondary to Lyme disease is considered to be transient and is expected to resolve with treatment of the underlying disease.5

While AV block is the most common cardiovascular manifestation of Lyme disease,6 patients may also present with

Figure 2. EKG on hospital day two showed second degree AV Block with 2:1 conduction.

Figure 3. The patient’s follow up EKG illustrates normal sinus rhythm.
myopericarditis, left ventricular dysfunction, cardiomegaly, pancarditis, aortitis, as well as ventricular tachyarrhythmias.\textsuperscript{4,7,8} The exact reason for variability in presentation is unknown, but is theorized to be secondary to the location and degree of spirochetal infiltration as evidenced by cardiac biopsies of non-human primates with Lyme disease.\textsuperscript{9} Histopathologic stains of these biopsies show infiltration of the \textit{Borrelia} spirochete from all regions of the heart, including aorta, atrium, and myocardium.\textsuperscript{9}

Because of the potential for life-threatening complications, hospitalization and continuous monitoring are advisable for symptomatic patients (e.g., those with syncope, dyspnea, or chest pain). These interventions are also suggested for patients with second or third degree AV block, as well as for those with first degree heart block when the PR interval is prolonged by more than 30 milliseconds because the degree of block may fluctuate and worsen very rapidly in such patients.\textsuperscript{12}

Patients with AV heart block and/or myopericarditis associated with early Lyme disease may be treated with either oral or parenteral antibiotic therapy for 14 days (range 14 to 21 days). For hospitalized patients, a parenteral antibiotic, such as ceftriaxone, is recommended as initial treatment, although there are no clinical trials to support this recommendation (Level of Evidence B-III).\textsuperscript{1} For patients with advanced heart block, a temporary pacemaker may be required; expert consultation with a cardiologist is recommended. The pacemaker may be discontinued when the advanced heart block has resolved. An oral antibiotic regimen should be used for completion of therapy and for outpatients, as is used for patients with erythema migrans without carditis.\textsuperscript{3}

### References


### Acknowledgements:

Stuart J. Gould, MD, Lan Quang, MD, and Samir Dalia, MD
A Man With Invasive Community Acquired-MRSA Infection in the ICU Setting
Jason Korenblit, MD, MBA

Case Presentation
A 66 year-old male presented to the emergency department (ED) with complaints of two days of shortness of breath and pruritis. The patient claimed that he had not had regular medical care for more than 15 years and admitted to no past medical history or chronic medications. One week prior, he reported an itchy rash on both his forearms. He sought treatment at a local free clinic and received a low-potency steroid cream which he used without relief. While at a family event, he became increasingly dyspneic and was brought to the ED by his family. He reported no surgical history and no drug allergies or food intolerances. The patient reported moderate alcohol use with one to two beers per day and denied any tobacco use, substance abuse, or intravenous drug use. He could report no pertinent family history.

On physical examination, the patient appeared mildly dyspneic and uncomfortable, but in no acute distress. He was afebrile, tachycardic with a pulse of 112 beats/minute, tachypnic with respirations of 32 breaths/minute, and normotensive. His lung exam revealed coarse breath sounds bilaterally with decreased respirations at the bases, but no wheeze, rhonchi, or cough. The cardiac exam was within normal limits except for the noted tachycardia, with no murmurs, rubs, or gallops. The abdominal exam revealed a freely reducible left inguinal hernia. Examination of the patient’s skin revealed an approximately 15-cm erythematous, non-blanching lesion on his posterior neck with some fluctuance as well as smaller, pustule lesions on his lower back, chest, and arms. The lesions were painless and fluctuant, with no exudates. He was drowsy but oriented, and had no focal neurologic deficits.

The patient’s white blood cell count (WBC) was high normal at 10.2 B/L, hemoglobin was low at 6.3 g/dL, hematocrit was 19.8%, and platelet count was elevated 534 B/L. The manual differential of the patient’s blood count revealed 61% neutrophils and 36% bands. The patient’s metabolic panel revealed an elevated potassium of 6.5 mmol/L, very low bicarbonate of 6 mmol/L, a greatly elevated BUN at 198 mg/dL and a greatly elevated creatinine at 17.8 mg/dL. The patient’s lactate was greatly elevated at 26.1 mg/dL. The patient’s ESR was 120 mm/hr. Prothrombin time was prolonged at 19.6 sec which corresponds to an INR of 1.57. Blood cortisol was 117.6 μg/dL. An initial venous blood gas revealed a pH of 7.23, a pCO2 of 14, a PO2 of 131, and a calculated bicarbonate of 7. Urinalysis revealed a WBC count of 187 per high-powered field, a RBC count of 9 cells per high-powered field, 3+ leukocyte esterase, and many WBC clumps. All other laboratory values including the hepatic function panel were within standard limits. An initial portable chest radiograph revealed questionable bibasilar infiltrates, but was limited by poor inspiratory effort.

The patient was admitted to the medical-respiratory ICU with acute renal failure and a suspected diagnosis of sepsis and community acquired pneumonia. His PORT score on admission was calculated at 176, which corresponds to the highest risk class of V and a greater than 2.8% in-hospital mortality. The patient was initially treated with aggressive fluid resuscitation, supplemental oxygenation, and the initiation of antibiotics. He received one gram of vancomycin and a renal-adjusted dose of pipericillin-tazobactam and gentamicin due to the severity of his condition. The patient also received kayexalate and several amps of sodium bicarbonate to offset his acidemia and hyperkalemia. Surgery was consulted for possible exploration and debridement of the lesion on the patient’s neck.

The morning following the patient’s admission to the ICU, initial blood and urine cultures were reported as positive for gram-positive cocci in clusters. A non-contrast chest CT (Figure 1) was obtained which demonstrated multi-lobar pneumonia with areas of cavitations as well as a large right pleural effusion and atelectasis. The patient’s oxygenation remained stable overnight, but his mental status began to deteriorate. The decision was made at this time to switch the patient’s antibiotics to linezolid given the severity of his cavitary pneumonia and the strong suspicion of *Staphylococcus aureus* infection.

Figure 1. Non-contrast chest CT demonstrating multi-focal cavitary pneumonia and extensive left pleural effusion

Over the next 18 hours the patient’s condition deteriorated despite aggressive intervention. Pharmacologic blood pressure support was initiated to combat this patient’s sepsis. His renal failure improved but his creatinine was still elevated at 12.6, and his BUN was 165. Bedside debridement of his neck lesion yielded copious amounts of necrotic material and brown, purulent liquid. Urine culture results returned with confirmation of methicillin-
resistant *Staphylococcus aureus* (MRSA), and while sensitivity results were not available yet, it was presumed to be community acquired. Infectious disease consultants advised to switch the patient back to vancomycin given the rapid development of sepsis and hypotension. Piperacillin-tazobactam was continued, and IV azithromycin was added for atypical pneumonia coverage. In addition, oral rifampin was added for synergistic treatment. Clindamycin was debated for its anti-toxigenic properties in the treatment of community acquired *MRSA* (CA-MRSA), but it was felt that the patient’s antibiotic regimen was adequate at the time.

All blood cultures, urine cultures, sputum cultures, and fluid cultures from the surgical debridement grew CA-MRSA within twelve hours of collection despite aggressive, optimal antibiotic treatment. A trans-thoracic echocardiogram revealed a vegetation on the patient’s mitral valve with severe damage to the valve and moderate mitral regurgitation. The patient was placed on a bicarbonate drip due to worsening acidemia, and bi-level positive airway pressure was initiated as a non-invasive means of ventilator support.

A meeting with the patient’s family was held where it was determined that further aggressive measures would be futile given the patient’s continued severe acidemia, renal failure, mental status deterioration, and need for surgical mitral valve replacement. Based on the patient’s prior stated wishes and those of his family, no further escalation of care was pursued. The patient expired less than 72 hours from his initial presentation of the ED.

**Background and Genetics**

*MRSA* was first described in Europe in the early 1960’s, several years after the introduction of the semi-synthetic beta-lactamase resistant penicillin, methicillin. It is defined as a *Staphylococcus aureus* isolate with a minimal inhibitory concentration for oxacillin of greater than 4 micrograms per ml. Approximately 50% of all *S. aureus* isolates in major teaching institutions are MRSA, resulting in extensive morbidity and mortality from their virulence and multi-drug resistance. A surveillance report of over 24,000 cases of nosocomial *S. aureus* bacteremia in the United States revealed that isolates with methicillin-resistance increased from 22% to 57% between 1995 and 2001. Worldwide, HA-MRSA prevalence varies considerably, from <1 percent in Scandinavia to up to 40% in Japan, Israel, and Western Europe.

By definition, all strains of MRSA are resistant to beta-lactam antibiotics, including all cephalosporins and extended-spectrum penicillins. The key to this resistance lies in the mec gene, which codes for a novel penicillin-binding protein (PBP 2a) that enables it to resist the binding of all beta-lactam antibiotics. PBP2a allows the bacterium to assemble its cell wall even in the presence of antibiotics, and the mecA gene complex is freely transmissible in a mobile gene element known as the Staphylococcal cassette chromosome (SCC-mec). In addition to this powerful resistance mechanism, many MRSA isolates produce beta-lactamases as well as various effluent pumps that protect the cell from multiple antibiotics. Five sub-types of the SCC-mec complex have been described; sub-types one, two, and three convey additional multi-drug resistance to quinolones, macrolides, and sulfa-based antibiotics and represent isolates of hospital-acquired *MRSA* (HA-MRSA). Sub-types four and five represent common CA-MRSA strains without multi-drug resistance, but with added virulence factors that make these strains especially dangerous.

Panton-Valentine leukocidin (PVL) is a unique compound found in CA-MRSA that may be responsible for the added virulence seen in these strains. It is a hemolysin that was first described by Panton and Valentine in 1932 that gives CA-MRSA the ability to cause necrotic skin lesions and predisposes for cavitary and hemorrhagic pneumonias, as seen with the index patient described above. PVL causes transcription-level changes in cells independent of other *S. aureus* toxins and cell products as purified extracts of PVL have been shown to cause pneumonitis in murine models even without the presence of infection. The ability of CA-MRSA to so readily infect immune-competent hosts may also be attributed to PVL. One recent study by Moran et al showed that 97% of CA-MRSA isolates identified at 11 university-affiliated emergency departments were found to produce PVL.

**Presentation and Epidemiology**

Presentation of CA-MRSA is usually as a skin and soft tissue infection, but it can cause invasive disease at any site including hematogenous osteomyelitis, septic arthritis, cavitary pneumonia, myositis and pyomyositis, and fasciitis; hematogenous osteomyelitis is the most common invasive infection. Fridkin et al found that 87% of cases of CA-MRSA at three community hospitals presented as skin and soft tissue infections or traumatic wound infections, 4% presented as urinary tract infections, 4% as sinusitis, 3% as bacteremia, and only 2% as community acquired pneumonia.

In a 2003 study by Naimi et al, 75% of cases of MRSA skin and soft tissue infection were due to CA-MRSA isolates, as opposed to nosocomial HA-MRSA which most commonly presented with bacteremia or catheter infections. A similar study in 2006 in Los Angeles indicated that a median of 59% of skin and soft tissue infections presenting to the emergency department were due to MRSA, over 95% of those were considered community acquired strains based on SCCmec genotyping, and 74% of MRSA isolates were strain U300, a common, PVL-producing strain.

Risk factors for acquiring a CA-MRSA include recent skin trauma, high body mass index, practice of cosmetic body shaving, male gender, participation in contact sports, prolonged hospitalization, incarceration, military service, diabetes, intravenous drug use, and history of a prior skin infection. No study has consistently shown risk factors that define MRSA infections
versus other skin and soft tissue infections; therefore empiric coverage should always be considered.10

Treatment
Treatment of CA-MRSA is oftentimes more straightforward since these particular strains do not exhibit multi-drug resistance that nosocomial MRSA innately display. Retrospective studies of CA-MRSA soft tissue infections have shown 95% were susceptible to clindamycin, 6% to erythromycin, 60% to fluoroquinolones, 100% to rifampin and trimethoprim-sulfamethoxazole (TMP-SMX), and 92% to tetracycline.9 Although proper antibiotic choice is an important part of treatment protocol to prevent further progression to invasive disease, the most important treatment of focal skin involvement is adequate drainage of any abscess or infectious collection. A 2007 prospective trial found that lack of incision and drainage was associated with significant non-response 30 days after initial treatment. Current CDC recommendations state that oral clindamycin or oral TMP-SMX should be first-line for empiric coverage of presumed CA-MRSA for all skin and soft-tissue infections identified.11

Intravenous antibiotic therapy for invasion MRSA, whether nosocomial or community acquired, centers on vancomycin and achieving appropriate therapeutic levels in target tissue. Vancomycin inhibits cell wall synthesis by preventing N-acetylmuramic acid (NAM)- and N-acetylglucosamine (NAG)-peptide subunits from being incorporated into the peptidoglycan matrix. It remains the antibiotic of choice for treatment of invasive MRSA infections, given its relatively good safety profile and favorable pharmacokinetics that facilitate convenient administration. In addition, vancomycin is the agent for which there is the greatest cumulative clinical experience for the treatment of a variety of invasive clinical syndromes including pneumonia, endocarditis, meningitis, and osteomyelitis.12 Reports of MRSA with either intermediate or full resistance to vancomycin or high in vitro resistance have spurred research for newer alternative agents.

Daptomycin is a novel intravenous agent used to combat MRSA and vancomycin-resistant enterococcus (VRE). It is a cyclic lipopeptide bactericidal antibiotic that causes depolarization of the bacterial cell membrane and is used for bacteremia, endocarditis, and soft-tissue infections due to invasive nosocomial and community acquired MRSA.13 Heteroresistance to daptomycin may develop during treatment, especially with co-exposure to vancomycin, so susceptibility testing may be necessary during treatment. Daptomycin is also activated by surfactant and is thus ineffective in treating pneumonia caused by MRSA.13

Linezolid is a bacteriostatic oxazolidinone antibiotic that inhibits initiation of protein synthesis at the 50S ribosome, and does not exhibit cross resistance with other protein synthesis inhibitors. Its mechanism of action may lead to enhanced efficacy against strains producing toxins such as PVL, alpha-hemolysin, and toxic-shock syndrome toxin-1, making it an excellent choice for initial therapy in severe cases of CA-MRSA.14 Linezolid has excellent tissue distribution, especially in the lung parenchyma, and may be administered parenterally or orally due to its high bioavailability.

Other potential treatment options include tigecycline, a novel tetracycline derivative that is active against most gram-positive infections. Tigecycline mono-therapy was deemed as effective as vancomycin plus aztreonam for complicated skin and soft tissue infections in a prospective randomized trial.15 Quinupristin-dalfopristin, a streptogramin antibiotic whose use is limited by side effect profile and high cost, has shown efficacy when used to treat patients who have failed vancomycin. One study by Drew et al showed 71% response in invasive infections in patients who could not tolerate or failed vancomycin therapy.16

Several investigational agents are undergoing trials. Dalbavancin is a semi-synthetic lipoglycopeptide that has been demonstrated to be at least as effective as vancomycin and linezolid, but has a half-life of six to twelve days and can be dosed once per week.17 Ceftobiprole is an extended-spectrum cephalosporin similar to cefepime that can circumvent PBP2a that confers beta-lactam resistance to MRSA. A randomized trial of 828 patients demonstrated efficacy similar to vancomycin plus ceftazidime.18 Preparations of staphylococcal antibodies have been investigated for the treatment of S. aureus bacteremia. Tefibazumab is a monoclonal antibody that targets clumping factor A, a protein on the surface of S. aureus that binds to human fibrinogen. Its current efficacy is debatable.19 Altastaph is an agent consisting of a pooled group of antibodies to S. aureus capsular polysaccharide types five and eight and may serve as an adjuvant therapy.20

Prevention
Prevention of CA-MRSA infection remains a community health challenge as few therapies have proven effective. No trial data supports the use of empiric nasal mupiracin or topical chlorhexadine rinse to prophylax against infection.12 Hand washing and avoidance of contact with infected individuals is key. Empiric treatment of close contacts of an infected individual is controversial, and no compelling data exists at this time. Pets have also been offered as a possible source of bacterial reservoir, and while transmission from an infected pet is possible, eradication therapy in household pets is not currently recommended.12

References
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Severe Heart Failure and Large Left Ventricular Thrombus Following Acute Myocardial Infarction

Ankitkumar K. Patel MD, MPH, Scott Silvestry, MD, and Paul J. Mather, MD

Case Presentation

A 58 year-old man who recently underwent a left superficial femoral artery thrombectomy presented with a three-day history of worsening exertional dyspnea and bilateral pedal edema. His past medical history is significant for coronary artery disease, myocardial infarction, and insulin dependent diabetes mellitus. The patient initially presented to an outside hospital where he developed ventricular tachycardia that warranted cardioversion three times. Initial electrocardiogram showed inferior lead ST segment elevations and lateral lead ST depression. The patient underwent a cardiac catheterization that showed triple vessel disease with total occlusion of the RCA, 90% occlusion of the LAD, and 50% to 60% occlusion of left circumflex. The patient had an echocardiogram (Figures 1 and 2) that showed severe left ventricular dysfunction with an ejection fraction of 10% and a large mobile thrombus occupying 60% of the left ventricular cavity and was diagnosed with a dilated cardiomyopathy. The patient underwent left ventricular thrombectomy (Figure 3), coronary artery bypass graft (i.e., a saphenous vein graft to LAD) and installation of a left ventricular assist device. The patient currently is doing well and is awaiting heart transplantation.

Discussion

An increased incidence of thromboembolism is seen in patients with left ventricular systolic dysfunction following myocardial infarction (MI). Following an acute MI, the formation of a left ventricular (LV) thrombus is a significant complication. LV thrombus occurs in up to one-third of patients with anterior wall MI and is much more frequent in patients with a large anterior MI and subsequent heart failure. The vast majority of LV thrombi are of the immobile mural type; unfortunately for our patient, he had the more rare mobile type which has a higher risk of embolism. LV thrombus has been associated with
dilated cardiomyopathy which leads to increased morbidity and mortality. The mechanism for the development of a mobile thrombus is not well understood. Moran et al hypothesize that an apical infarction involves the detachment of one end of the trabecula of the left ventricle which acts as a nidus for thrombosis. Prompt surgery is warranted once a mobile thrombus is identified. Left ventricular thrombectomy and coronary artery bypass graft surgery after an acute MI have increased risks. In order to improve the clinical status of our patient, he had a left assist device inserted during the surgery to help reduce the LV workload and provide a bridge to cardiac transplantation.

References
Jaundice in a Leukemia Patient Status-Post Allogeneic Stem Cell Transplantation

Esther Lee, MD

Case Presentation

A 61-year-old Caucasian female with a past medical history significant for chronic lymphocytic leukemia (CLL) presented with dark amber-colored urine, jaundice, and nausea for three days. She reported increased fatigue and poor appetite but denied fever, chills, shortness of breath, chest pain, vomiting, abdominal pain, diarrhea, constipation, or bleeding. She denied any change in her medications or recent travel history.

She was diagnosed with CLL two years ago and had undergone a matched unrelated allogeneic stem cell transplant three months ago. Her post transplant course was complicated by viremia with cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which were successfully treated with foscarnet and rituximab, respectively.

Other past medical history included hypertension and basal cell carcinoma of the face. Past surgeries included a cholecystectomy, a hysterectomy, and bilateral knee replacements. She denied alcohol use, smoking, or drug abuse. Medications on admission included atenolol, a multivitamin, trimethoprim/sulfamethaxazole, voriconazole, and valacyclovir. She was allergic to codeine and lorazepam.

Vital signs on admission were stable. Physical exam was significant for icteric sclera, jaundice, and mild abdominal discomfort on palpation of the right upper quadrant. Admission labs were notable for total bilirubin 14.9 mg/dL, direct bilirubin 7.2 mg/dL, alkaline phosphatase (AP) 421 IU/L, aspartate transaminase (AST) 558 IU/L, and alanine amino transferase (ALT) 738 IU/L. White blood cell count was 3 B/L with 75% neutrophils, hemoglobin was 9.5 g/dL, and platelet count was 124 B/L. Her basic metabolic panel was within normal limits. Her urinalysis was significant for 1+ bilirubin.

Jaundice and abnormal hepatic function tests in this patient with the history of CLL and allogeneic stem cell transplant raised concerns for active hepatitis, graft-versus-host disease (GVHD) of the liver, drug toxicity, hepatic veno-occlusive disease, and obstructive cholestasis.

Hospital Course

The patient underwent an abdominal ultrasonography with dopplers that showed a normal liver status-post cholecystectomy with no intrahepatic or extrahepatic ductal dilatation and normal hepatic vasculature, ruling out obstructive cholestasis and hepatic veno-occlusive disease. With her history of CMV and EBV viremia, it was crucial to rule out residual or recurrence of either infection. Her CMV viral load was less than 100 copies/ml (reference range <100 copies/ml), and EBV viral load was less than 350 copies/ml (reference range <350 copies/ml). Further laboratory studies for Hepatitis A, Hepatitis B, and Hepatitis C were all negative. Adenovirus, which has been increasingly known to cause disease in post transplant patients, was also negative. A transjugular liver biopsy was done since there was no obvious cause of elevated liver function tests from the available laboratory studies. The liver biopsy revealed mild portal inflammation and bile duct injury characteristic of GVHD with moderate cholestasis.

With the diagnosis of GVHD of the liver, the patient was immediately started on immunosuppressive therapy which included high-dose methylprednisolone, tacrolimus, and micophenolate mofetil. Although she continued to have minimal clinical symptoms other than jaundice, she failed to show significant improvement in her hepatic function tests. By hospital day 15, the laboratory results were as follows: total bilirubin 39.1 mg/dL, direct bilirubin 17.8 mg/dL, AP 557 IU/L, AST 151 IU/L, and ALT 355 IU/L. While her transaminases were trending down, total bilirubin, direct bilirubin, and AP were worsening. Without much improvement with the conventional immunosuppressive therapy, a monoclonal antibody called muromonab or OKT3 was added. Muromonab, which is a monoclonal antibody directed against the CD3 antigen closely associated with the T-cell receptor, has been used as a second line therapy in patients who did not respond to steroids for GVHD. Even after the treatment with muromonab for 10 days, her hepatic function tests did not improve significantly: total bilirubin 30.3 mg/dL, direct bilirubin 12.7 mg/dL, AP 436 IU/L, AST 78 IU/L, and ALT 104 IU/L. She was discharged with oral corticosteroids for continued treatment of her GVHD of the liver. At this time, it is difficult to predict whether she will recover completely from the GVHD. Of note, the treatment of her GVHD was complicated by a rise in her CMV viral load on day 24 of her hospital stay to 375 copies/mL and clostridium difficile enterocolitis.

Discussion

Hematopoetic stem-cell transplantation is an important and common treatment in malignancies and multiple hematologic disorders. In the early 1960s, allogeneic transplantation became feasible after the identification and typing of HLA, the major histocompatibility complex. In the 1970s, Thomas and colleagues conducted successful allogeneic stem cell transplants in end-stage leukemic patients and achieved first remissions in more than half of their patients, thus laying a foundation for use of this treatment in conjunction with conventional chemotherapy and radiation.

When allogeneic stem cell transplantation takes place, unsuppressed donor T-cells can recognize either major histocompatibility or minor histocompatibility antigens of a recipient, which leads to the activation of the donor T-cells against the recipient’s organs. This phenomenon is also known as graft-versus-host disease (GVHD).
GVHD that occurs within 100 days after transplantation is considered acute GVHD, as was the case for this patient. GVHD that occurs after 100 days is considered chronic. Both types of GVHD occur more frequently with cases involving older patients, unrelated donors, older donors, CMV-positive donors, female donors, and donors with previous pregnancies or transfusion sensitization. Clinically significant GVHD happens in 30% to 50% of recipients of allogeneic hematopoietic transplants.

The primary target organs in GVHD are the skin, liver, gastrointestinal tract, and the hematopoietic system. The liver is the second most commonly involved organ in acute GVHD, and manifests with abnormal liver function tests. The earliest and most common finding is the rise in direct bilirubin and alkaline phosphatase, which is explained by the fact that GVHD causes damage to bile canaliculi and results in cholestasis. The rise in direct bilirubin and alkaline phosphatase is nonspecific, however, so other causes of hepatic damage require evaluation. Hepatic infections, primarily viral hepatitis, must be ruled out since many of these patients are immunocompromised and are at an increased risk of infection. Another important diagnosis to consider is hepatic veno-occlusive disease, which is characterized by obstruction in the hepatic circulation as result of damaged sinusoidal endothelium. Total-body irradiation and chemotherapy that are used as preparative agents for stem cell transplant are the cause of this relatively common complication. Patients with hepatic veno-occlusive disease present with painful hepatomegaly, jaundice, and retain fluid. Another diagnosis to consider is drug toxicity from chemotherapeutic drugs, corticosteroids, antibiotics, antifungal agents, and anti-GVHD drugs. Biopsy is the definitive method to diagnose GVHD of the liver, and trans jugular liver biopsy may be preferable over percutaneous liver biopsy due to the high bleeding risk since many of these patients are thrombocytopenic. Transjugular biopsy may be also helpful in assessing the hepatic venous pressure gradient to identify hepatic veno-occlusive disease.

The first and most effective treatment of GVHD is the use of glucocorticoids. Research suggests that starting with low dose steroids (2mg/kg per day) is appropriate; randomized studies showed no difference in mean response rates or actual survival rates between different dosages of steroids. If glucocorticoids are not successful, other immunosuppressive drugs such as cyclosporine, tacrolimus, antithymocyte globulin, or mycophenolate mofetil may be considered. If these treatment strategies fail, then a more aggressive approach such as using extracorporeal photophoresis and monoclonal antibodies directed against CD 25, TNF-alpha, T-cell receptor, and IL-2 receptor may be considered.

In summary, this is a case of a 61 year-old female with a history of CLL status-post allogeneic stem cell transplant who presented with jaundice and a rise in bilirubin and alkaline phosphatase on laboratory testing, which raised concerns for possible GVHD of the liver. However, it was very important to consider all other disease possibilities. Especially in this case, a distinction between an active infection versus graft-versus-host disease was crucial as immunosuppressive therapy would have worsened the patient’s condition if the cause had been an active infection. The patient underwent a transjugular liver biopsy that was consistent with the GVHD of the liver, and she has been on different regimens of immunosuppressive drugs. The immunosuppressive therapy for the GVHD led to the complications of elevation of the CMV viral load and clostridium difficile infection, which highlights the fact that sometimes medicines intended for treatment can in effect cause harm. This reinforces the lesson to always weigh the benefits against the risks when choosing to implement a therapy.

References
A 57 Year-old Man With Prolonged Shortness of Breath and Fevers

Loren Chen, MD

Case Presentation
A 57 year-old Caucasian male was initially admitted to Methodist Hospital from an outside hospital for dehydration, increased heart rate, and weight loss. He has a past medical history of coronary artery disease status post myocardial infarction and coronary artery bypass graft, congestive heart failure, paroxysmal atrial fibrillation on coumadin, diabetes type II on insulin, and an orthotopic liver transplant in 1997 for end-stage liver disease secondary to hepatitis C virus and alpha-1 antitrypsin disorder.

At the outside hospital, his one-month hospital course was complicated by acute on chronic renal failure which warranted hemodialysis, anemia that required transfusions, MRSA line sepsis from his Perm-A-Cath treated with vancomycin, and pneumonia, which was possibly secondary to aspiration. The patient was transferred to our facility for further management.

Additional past medical history is significant for hyperlipidemia, depression and C3 to C5 fracture. Additional surgeries include AICD placement, a C3 to C4 diskectomy, cholecystectomy and appendectomy. Social history was negative for alcohol and substance abuse, but positive for a 30 pack year smoking history, which he quit one year ago. Family history was significant for diabetes, coronary artery disease and lung cancer. Current medications included amiodarone, aspirin, carvedilol, nexium, zetia, insulin, nebularizers, sirolimus, vancomycin, zosyn, and gentamicin. His only allergy was to meperidine.

Initial vital signs were temperature 98.9˚ Fahrenheit, pulse 77 beats/minutes, respirations 16 breaths/minute, blood pressure 126/70 mm Hg, oxygen saturation 99 % on room air. The patient was in no acute distress. Physical exam was significant only for bilateral crackles at the lung bases, multiple skin tattoos, a right-sided Perm-A-Cath in the chest that was non-tender without surrounding erythema or swelling, and a surgical scar in the right upper quadrant.

Chest radiograph on admission showed a right lower lobe consolidation, and he was continued on antibiotics for presumed pneumonia. The patient appeared to be improving after finishing his course of antibiotics for line sepsis and suspected pneumonia, and plans were made to transfer him to a subacute rehab with outpatient dialysis. One week after hospital transfer, he developed fevers and chills with accompanying shortness of breath. Blood cultures grew out pan-sensitive E. coli from his Perm-A-Cath. The catheter was removed and a Shiley catheter was placed. After completing a course of antibiotics, he remained afebrile, and when his blood cultures showed no growth for 48 hours, another Perm-A-Cath was placed. However, he became febrile again. A repeat chest radiograph showed increasing left lingular pneumonia in addition to an unchanged right lower lobe consolidation (Figure 1). At this point, he finished a course of empiric moxifloxacin which was recommended by the infectious disease service.

He continued to have intermittent fevers, shortness of breath, a non-productive cough, and hypoxia that required oxygen therapy. Prior to this prolonged hospitalization, the patient was able to breath on room air. Serial chest radiographs showed increasing pulmonary infiltrates despite treatment with a triple antibiotic regimen. At this time, physical exam was only remarkable for bibasilar, course crackles, but no wheezes or rhonchi. He had a trans-thoracic echocardiogram that was negative for endocarditis, a CT of the abdomen and pelvis that was negative for abscess, and a chest CT that showed persisting bilateral lower lobe pulmonary opacities, left greater than right, and scattered abnormal mediastinal lymph nodes (Figure 2). Cultures were negative since his episode of E. coli bacteremia, and labs were unremarkable.

A bronchoscopy showed normal airways and no endobronchial lesions. Biopsies and bronchial alveolar lavage (BAL) were taken from the superior segment of the left lingua. The BAL revealed numerous foamy, hemosiderin-laden macrophages, and the biopsy revealed interstitial pneumonia consistent with amiodarone-induced lung toxicity. Stains were negative for malignant cells.

Amiodarone and antibiotics were stopped, and the patient was started on prednisone 50 mg PO once daily (1mg/kg/day) with a taper to 20 mgs per day as his infiltrates cleared. Within one week of treatment, his fevers resolved with near resolution of his respiratory symptoms by the time of transfer to rehab. His vasculitis labs including ANCA, ANA, ESR, double-stranded DNA, anti-Jo, RF, anti-GBM and IgA, were negative. Further tests for Legionella, AFB, respiratory viruses, hepatitis B, HIV, CMV, and EBV were negative. In regards to his atrial fibrillation, since amiodarone was discontinued, his carvedilol was increased, and...
the patient remained in sinus rhythm throughout the rest of his hospitalization.

A follow-up chest CT two months later revealed significant improvement of his infiltrates and ground glass opacities.

Discussion

Although amiodarone is approved by the Food and Drug Administration only for refractory ventricular arrhythmias, it is one of the most frequently prescribed antiarrhythmic medications in the United States. According to a large evidence-based review, amiodarone has clinical value in patients with left ventricular dysfunction and heart failure as first-line treatment for atrial fibrillation and acute management of sustained ventricular tachyarrhythmias. It can have a prophylactic role during the perioperative period of cardiac surgery and may be an effective adjunct to implantable cardioverter-defibrillator therapy to reduce the number of shocks. However, adverse side effects are common and include corneal microdeposits (>90%), optic neuropathy/neuritis (<1% to 2%), blue-gray skin discoloration (4% to 9%), photosensitivity (25% to 75%), hypothyroidism (6%), hyperthyroidism (0.9% to 2%), peripheral neuropathy (0.3%), hepatotoxicity (15% to 30%), hepatitis and cirrhosis (<3%), and pulmonary toxicity (1% to 7%).

Figure 2. Chest CT shows persistent bilateral lower lobe pulmonary opacities, left greater than right, extending to the periphery.

Figure 3. Two month follow-up chest CT shows resolving infiltrates and ground glass opacities.
Amiodarone was initially developed in the 1960s as an antianginal agent due to its vasodilatory properties and serendipitously was found to suppress arrhythmias. Despite widespread use for nearly two decades in Western Europe, there were no reported cases of associated pulmonary toxicity until 1980, after it was introduced as an investigational agent in this country. This was initially thought to be due to the higher doses used for ventricular arrhythmias, but retrospective analysis revealed that cases had been observed in Europe, but were missed. Currently, amiodarone-induced pulmonary toxicity (APT) carries a mortality between 21% to 33% of patients who are admitted to the hospital.

The cause of APT is not well understood. Amiodarone and its metabolite, desethyl-amiodarone (DEAm), are amphiphilic cations which accumulate in tissues, including the lung. It can also infiltrate into the liver, skin, thyroid, and eye, which are other common sites for adverse effects. In regards to pulmonary toxicity, amiodarone can damage lung tissue directly via a cytotoxic process and indirectly via immunological reactions, supported by findings of CD-8-positive, cytotoxic T cells on bronchoalveolar lavage often in combination with polymorphic nuclear cells, increased production of toxic oxygen radicals, and accumulation of phospholipids complexes which interfere with normal cellular metabolic pathways.

Risk factors for developing APT are increased age, pre-existing lung disease, recent pulmonary insults, cardiopulmonary surgery involving oxygen given at high concentrations, and dosages greater than 400mg/day. It is more frequent in men and unusual in patients younger than 40 years old, though rare case have been described in children. Most amiodarone-induced pulmonary manifestations are found to occur when the dosage exceeds 400mg/day administered for more than 2 months or when a lower dosage is given for more than 2 years. However, APT has been noted to occur in lower doses, albeit not as frequently.

On average, pulmonary toxicity will develop in 5% to 15% of patients who take 500mg/day or more and 0.1% to 0.5% who reduce the dosage to its lowest effective level, though pulmonary toxicity has been noted to still occur at such doses. Other options include radiofrequency ablation of a causative re-entry mechanism and implantation of an automatic cardioverter defibrillator. Despite the lack of controlled studies, there is a few days after an initial loading dose to more than a decade following thoracic surgery, open or thoracoscopic lung biopsies are indicated when an accurate diagnosis is required early for example, in patients in whom amiodarone cannot be held without risks, if a diagnosis of pulmonary opacities is required prior to heart surgery, and in patients who do not improve by one to two months after drug cessation and initiation of steroids to evaluate for other causes.

In summary, one should consider the diagnosis of APT in the presence of three or more of the following: new or worsening symptoms or signs, new abnormalities on chest imaging, a decline in the total lung capacity >15% or Dl CO >20%, presence of phospholipidosis in lung cells, a marked CD8+lymphocytosis in lavage fluid, a lung biopsy that reveals diffuse alveolar damage, organizing pneumonia, interstitial pneumonitis, or fibrosis, and improvement in respiratory status following withdrawal of the drug with or without steroid therapy.

Treatment of APT consists primarily of discontinuing amiodarone. This can, however, lead to an increased risk of recurrence of life-threatening arrhythmias. One option is to substitute another antiarrhythmic medicine though it may have more negative inotropic and proarrhythmic effects. Another option is to withhold amiodarone for several days, and then, reduce the dosage to its lowest effective level, though pulmonary toxicity has been noted to still occur at such doses. Other options include radiofrequency ablation of a causative re-entry mechanism and implantation of an automatic cardioverter defibrillator. Despite the lack of controlled studies, there is a few days after an initial loading dose to more than a decade following thoracic surgery, open or thoracoscopic lung biopsies are indicated when an accurate diagnosis is required early for example, in patients in whom amiodarone cannot be held without risks, if a diagnosis of pulmonary opacities is required prior to heart surgery, and in patients who do not improve by one to two months after drug cessation and initiation of steroids to evaluate for other causes.

In summary, one should consider the diagnosis of APT in the presence of three or more of the following: new or worsening symptoms or signs, new abnormalities on chest imaging, a decline in the total lung capacity >15% or Dl CO >20%, presence of phospholipidosis in lung cells, a marked CD8+lymphocytosis in lavage fluid, a lung biopsy that reveals diffuse alveolar damage, organizing pneumonia, interstitial pneumonitis, or fibrosis, and improvement in respiratory status following withdrawal of the drug with or without steroid therapy.
growing evidence that corticosteroids are beneficial. The current recommendations are to start with an adequate dose of 0.75 to 1mg/kg of prednisolone or equivalent. The initial dosage should then be maintained until definite clinical and radiographic response is obtained, otherwise consider increasing the dose. Tapering should be slow since recurrences have been described up to eight months of cessation of therapy. A reasonable estimate of duration of treatment is six months, more often one year, and patients should be monitored carefully after discontinuation of corticosteroids for possible recurrence. Clinical improvement and clearing of pulmonary opacities typically require one to three months. Toxic effects may continue and even temporarily progress because of its persistence in the lung and accumulation in fatty tissues leading to a long half-life of up to 45 days.2, 4, 5

References

Photograph courtesy of Lisa Teng, MD
A 61 Year-old Man With Delayed Hypersensitivity Reaction to Joint Prosthesis
Regina C. Lee, MD

Case Presentation
61 year-old male with a past medical history of coronary artery disease complicated by myocardial infarction in 1984, type 2 diabetes mellitus, hyperlipidemia, hypertension, and right total knee replacement in 2006 presents to the outpatient allergist’s office for evaluation. The patient reports that he never fully recovered after the knee surgery and never regained function. The right knee remained swollen and painful with limited range of motion and weight bearing as a result. He denies any rash, redness, or itching in the area. He also denies any history of reactions to metals in the past. The orthopedic surgeon referred the patient to an allergist to assess for an allergic reaction to various components of the orthopedic hardware prior to the right knee revision surgery.

The patient has no known drug allergies. His medications include insulin 70/30 at breakfast and dinner, diltiazem CD 360 mg daily, simvastatin 20 mg daily, lisinopril 10 mg daily, metoprolol 12.5 mg twice daily, nitroglycerine patch for 12 hours daily, alprazolam 5mg three times a day for anxiety, and naproxen and percocet as needed for pain. The patient is a lifetime non-smoker and stopped drinking alcohol over 20 years ago. Family history is significant for coronary artery disease and prostate cancer. There is no family history of asthma or allergy.

At the initial visit, the patient was afebrile with stable vital signs. The physical exam was unremarkable except for right knee swelling, decreased range of motion, a well-healed midline scar, and 1+ edema of the right lower extremity up to the knee. The knee was non-tender and no warmth or erythema was noted.

To evaluate for delayed hypersensitivity reaction, a panel of allergens using the Thin-layer Rapid Use Epicutaneous (TRUE) patch test were placed on the patient’s skin. A vitallium metal disk, a known component of the prosthesis, was also placed on the patient’s skin. At 48 hours, the patch test was clearly positive for black rubber and possibly positive for potassium dichromate and Balsam of Peru. Since the patch did not stay entirely adherent to the skin, the adhesive was reinforced and the patient was instructed to return the next day for a 72-hour reading. At the second reading, the test remained strongly positive to black rubber. In addition, potassium dichromate showed strongly positive reaction, and cobalt dichloride showed weakly positive reaction. Upon re-examination, the reaction to Balsam of Peru appeared more likely to be irritation and not a true reaction. Given that the patient’s knee prosthesis was composed of 30% chromium, suspicion for metal allergy to the prosthesis was high. The finding was communicated to the orthopedic surgeon for consideration in further management of the patient’s condition.

Discussion
Metal hypersensitivity is common in the general population and often manifests as contact dermatitis to various everyday items including jewelry, watches, and belt buckles. The exposure may also occur in the form of metal ions dissolved in food and water. If ingested, metal ions can cause similar dermatological reactions or more systemic reactions such as asthma-like symptoms. The most common metal hypersensitivity is to nickel, followed by cobalt and chromium. Nickel and cobalt show significant cross-reactivity.

Metal allergy involves the type IV hypersensitivity response, also known as the cell-mediated delayed-type hypersensitivity (DTH). In DTH reaction, antigens are taken up and expressed on antigen presenting cells (APCs) which activate sensitized T1 lymphocytes, a subpopulation of T-cells. The T-cells then release various cytokines, which in turn recruit and activate macrophages, monocytes, neutrophils, and other inflammatory cells. Activated macrophages can trigger the activation of more T-cells, perpetuating the inflammatory response and leading to extensive tissue damage. Metals or metal ions on their own are not known to activate the immune system. Rather, it is the metal-protein complexes, formed by the degraded metal products binding to the native proteins, that can function as antigens and elicit an immune response. Specific APCs and T-cell receptors implicated in the DTH responses to metal are yet unidentified, and the current management for metal hypersensitivity is mainly based on exposure avoidance.

Metal prostheses, as with all metal exposed to biological environment, are known to corrode over time and release wear debris into the joint space. Nickel and cobalt ions seem to clear rapidly from the synovial space and are eliminated in the urine, but chromium appears to be stored in the tissue and eliminated more slowly. Concern for metal hypersensitivity to joint prosthesis was first raised in several case reports from the early 1970s, which noted that some patients with metal-on-metal joint replacement developed reactions that may be allergic in nature. Since then, implant-related metal hypersensitivity has been documented in numerous case reports and cohort studies. Still, as a clinical entity, it is only loosely characterized and poorly understood.

Commonly reported findings include eczematous rash, either generalized or on the skin overlying the orthopedic implants, along with discomfort, pain, erythema, and swelling over the affected joint. Some patients also report malaise, fatigue, and general weakness. Most concerning of all, DTH to metal prostheses has been cited as at least partially responsible for “aseptic loosening” of the prosthetic joint, in which chronic inflammatory-mediated osteolysis around the implant leads to loss of fixation and eventual implant removal. In suspected cases of implant-associated DTH reactions, the synovial fluid tends to be culture negative and have only few leukocytes. Histologically, inflammation and oligoclonal T-cell infiltrates are present in the peri-implant tissue, indicating an immune-mediated process, and cytokines typical of DTH, such as IL-6 and INF-γ, are expressed in high concentrations.

The conventional method of diagnosing metal hypersensitivity is by patch testing, in which a panel of antigens is exposed directly onto the skin for 48 to 96 hours, and the resulting dermatological
reactions are graded.³ It is a less-than-ideal method since the skin is a natural barrier that protects the immune system from antigen exposure. In the case of implant-associated metal hypersensitivity, patch testing is even more unreliable since the synovial cavity has a different cellular and biochemical composition than the skin.² Furthermore, there is at least the theoretical concern that patch testing could induce a hypersensitivity reaction in previously insensitive patient.³ Several in vitro studies for testing DTH are available, although their value specifically in implant-associated metal hypersensitivity has not been studied extensively.

Lymphocyte transformation testing (LTT) measures the proliferative response of lymphocytes to a designated challenge antigen.³ Leukocyte migration inhibition testing (LIF or MIF) measures the migration of lymphocytes on a culture medium in the presence of a sensitizing antigen which tends to inhibit migration.³ Unfortunately, both LTT and LIF are labor-intensive and lack the sensitivity and specificity to be reliable in the clinical setting. At this time, diagnosis of implant-associated metal hypersensitivity is largely based on clinical presentation and exclusion of other etiologies.

Can patients be screened for metal allergy prior to undergoing joint replacement surgery? Some studies have suggested that patients with documented metal allergy have more symptoms of implant-associated DTH and that positive patch test to metal is more common in patients with failed joint prostheses than in those with well-functioning prostheses.¹ However, studies that looked at pre- and postoperative sensitization to metal showed that a significant number of patients develop metal sensitivity postoperatively.²,³,⁴ Furthermore, only a fraction of those with positive patch test, both pre- and postoperatively, developed clinical manifestations of DTH to metal implants.²,³,⁴ In fact, many of those with positive patch tests had no history of reaction to metal. Studies that used in vitro tests independently or in combination with the patch test also failed to produce any consistent findings. At this point, there is no reliable method to assess for implant-associated metal allergy preoperatively.

Since DTH does not involve the histamine-release pathway, the common allergy medications are ineffective in treating metal prosthesis allergy. Low-dose corticosteroids have been used as a temporary solution, but their numerous adverse side effects deem them inappropriate for long term treatment.⁷ As with the cutaneous form of metal hypersensitivity, the definitive treatment for implant-associated metal hypersensitivity is elimination and avoidance, or, in other words, surgical removal of the metal prosthesis. Although removal of the offending prosthesis generally leads to complete and prompt healing, the revision surgery is obviously a serious undertaking. Biologically more inert materials are under investigation as alternatives to the currently available metal prostheses. Also, research is underway to determine genetic polymorphisms for factors involved in DTH and to develop targeted immunosuppressive agents.⁴ Implant-associated metal hypersensitivity is an extremely rare condition. However, in those few who are affected the consequences are grave. The condition is probably under-recognized and under-reported due to the difficulty of diagnosis. More research, including longitudinal prospective studies, are needed to better understand this immunological, rheumatological, and surgical enigma.

References
Primary Care Follow Up Post Mitral Valve Surgery at Ambulatory Clinic

Andrew Yin, MD

Case Presentation
A 67-year-old Cantonese speaking male was seen at primary care clinic with complaints of dyspnea on exertion and decreased exercise tolerance. His medical history includes rheumatic heart disease, tricuspid regurgitation, tricuspid repair three months ago, mitral regurgitation, mitral valve replacement with a bioprosthetic valve three months ago, atrial fibrillation on anticoagulation therapy, permanent pacemaker implantation, severe pulmonary hypertension, benign prostatic hypertrophy, gastroesophageal reflux disease, and iron deficiency anemia.

The patient reports that in the last two weeks, he has been unable to ambulate more than two blocks limited by shortness of breath, which represents an acute change. He also complains of bilateral lower extremity edema. He reports that two weeks after his mitral valve replacement, his exercise tolerance was dramatically improved, and he was able to ambulate more than two blocks without difficulty.

The patient also had an appointment with his cardiologist for evaluation of his symptoms. After the evaluation he was admitted directly to hospital for further evaluation of his new symptoms of congestive heart failure. His admission labs were unremarkable with the exception of B-type natriuretic peptide of 1463 pg/mL. His admission chest x-ray was suggestive of a left pleural effusion, cardiomegaly and pulmonary edema.

Transthoracic echocardiogram revealed the bioprosthetic valve in the mitral position had its ventricular side tilted toward the interventricular septum. There was no evidence of rocking of the mitral prosthesis. The peak mitral valve gradient was 13 mm of Hg. The mean transmural valve gradient was 4 mm of Hg. The estimated mitral valve area was 2.6 cm² which is described as normal in the setting of a prosthetic valve. There was a moderate paravalvular regurgitant leak between the prosthesis and lateral wall of the left ventricle (LV). The effective regurgitant orifice area of the paravalvular leak is estimated at 0.33 cm². There was evidence of mild aortic regurgitation, mild left atrial enlargement and an overall severely decreased LV systolic function with segmental wall motion abnormalities. The distal half of the LV is akinetic. The proximal walls were severely hypokinetic. LV ejection fraction was estimated to be 20%, and there was right ventricular (RV) enlargement with decreased function. There was no evidence of vegetation on the valves or pacemaker leads. Compared with an echocardiogram done one month following replacement, of his mitral valve, there was interval deterioration of LV function. The paravalvular leak appeared unchanged.

Computed tomography of the thorax without contrast demonstrated an irregular consolidation in right upper lobe which was indeterminate, but most likely represented atelectasis and/or pneumonitis, bilateral pleural effusions, a left lower lobe consolidation and an enlarged left heart post mitral and tricuspid valvular repair.

Cardiothoracic surgery was consulted. Due to the malpositioning of the prosthetic valve and evidence of worsening ventricular function, it was decided that the patient would need another operation to replace his prosthetic mitral valve.

Discussion
Heart valve surgery is still considered one of the most important advances in patients with symptomatic, severe valvular heart disease. Annually, there are an estimated 42,000 mitral valve procedures in the United States. It is important to appreciate that replacement of a diseased valve is not a cure for the valvular disease process, but rather an exchange of the native disease for a new set of complications that are associated to the new valve prosthesis. For this reason, the frequency and intensity of follow up and evaluation of prosthetic valves is similar to the follow up of newly diagnosed native valve disorders. The American College of Cardiology (ACC) and the American
Heart Association (AHA) Task Force recommends the following guidelines for evaluation and management of patients after valve replacement:

The first postoperative outpatient evaluation should be two to four weeks after hospital discharge. By this time, the patient’s physical capabilities and expected improvement in functional capacity can be assessed. The focus of this initial evaluation is to assess for infection and myocardial infarction, an assessment of function of the prosthetic valve, electrical conduction and other valvular disorders. Follow up should include an interval post-op history, physical examination, an electrocardiogram, complete blood count, electrolytes, an INR as indicated for management of anticoagulation therapy and a transthoracic Doppler echocardiogram. Echocardiography can provide information about prosthesis stenosis or regurgitation, valve area, pulmonary hypertension, LV or RV hypertrophy, LV and RV size and function, pericardial effusion and thickening, perivalvular regurgitation and assess function of the other heart valves. This initial echocardiogram is important to establish baseline characteristics of the prosthetic valve if one was not yet done prior to discharge.

Follow up of asymptomatic patients should be conducted annually. No further echocardiographic testing is required after the initial postoperative evaluation in patients who are stable and do not have symptoms or clinical evidence of LV dysfunction, prosthetic valve dysfunction, or dysfunction of other heart valves. Reevaluations should be conducted if there is any change in clinical status or development of new symptoms. An echocardiogram is indicated in any patient whenever there is evidence of a new murmur or change in clinical status, when there are questions about prosthetic valve integrity and function, and when there are concerns about ventricular function. If the patient develops valvular regurgitation, close follow up with echocardiography every three to six months is indicated.

Patients who do not improve after surgery or who later show deterioration of functional capacity should be evaluated with an echocardiogram and, if necessary, transesophageal echocardiography and cardiac catheterization with angiography to determine the cause.

Prosthetic heart valves are associated with a number of complications including structural failure or deterioration, valve obstruction from thrombosis, systemic embolization, bleeding, endocarditis, impaired LV systolic function, hemolytic anemia, and other infections. Perivalvular leakage, a form of structural failure, is common. Severe perivalvular regurgitation maybe inaudible on physical exam. Most are detected intraoperatively during the original valve surgery. Rates are reported to be between 18 to 48%. The majority of perivalvular leaks are trivial and are not clinically significant and do not progress. Our patient’s work up revealed that not only was his prosthetic mitral valve malpositioned, but also his echocardiogram showed an interval decline in his left ventricular systolic function three months after operation.

Re-operation to replace a prosthetic heart valve is a considered serious clinical event. The ACC/AHA Task Force recommends re-operation for moderate to severe prosthetic dysfunction (structural and nonstructural), dehiscence, and prosthetic endocarditis. Other indications include patients who have recurrent thromboembolism, severe intravascular hemolysis, severe recurrent bleeding from anticoagulant therapy, and thrombosed prosthetic valves. Stable patients without prosthetic valve endocarditis under many circumstances who requires reoperation are only slightly greater operative risk compared to the risk of the initial surgery. In patients with catastrophic prosthetic valvular dysfunction, surgery is clearly indicated and urgent. Patients without endocarditis or severe prosthetic valve dysfunction require careful hemodynamic evaluation, and the decision about reoperation should then be based on hemodynamic abnormalities, symptoms, ventricular function, and the natural history of the particular prosthesis.

In summary, patients who undergo mitral valve replacement for treatment of their disease are not completely cured of valvular heart disease and must be followed with the same care as patients with native valve disease. A number of post-operative complications are common and may develop early or late in the post-operative period. The ACC/AHA Task Force on the management of valvular heart disease recommends close annual

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**Figure 1.** The patient's chest radiograph shows cardiomegaly, pulmonary vascular congestion, developing consolidation in left lower lobe, a left-sided dual chamber pacemaker, midline sternotomy wires, and evidence of a tricuspid annuloplasty ring.
evaluation and a baseline echocardiogram initially to monitor valve structure and function. Though patients generally follow up with subspecialists for evaluation of their prosthetic valves, our patient sought all of this medical and post-operative care with his primary care physician because of language and cultural barriers. It is therefore critical that primary care physicians also recognize the signs and symptoms of the serious complications related to prosthetic valves.

**Hospital Course**

On day five of his hospital course, the patient was brought to the operating room for a replacement of his prosthetic valve. It was discovered that the patient had three major defects. The first was a 0.5 cm defect near the mitral-aortic continuity with the surgical pledgets having torn through the annulus with subsequent partial dehiscence of the prosthetic mitral valve. The tissue around the dehiscence was friable and could not be repaired. The prosthesis was excised and replaced. The second defect was a linear tear below the left coronary cusp of the aortic valve that disrupted the aortic ventricular continuity. The defect could not be repaired and thus was also replaced. Lastly, the third defect was a tear of the pericardium which was repaired using a sheet of bovine pericardium. Intraoperatively, the patient continued to have significant bleeding from behind the aortic root and was treated with various hemostatic agents including Biogel and Surgicel. He required multiple vasoactive medications and required multiple units of blood products but continued to be hemodynamically unstable with a pressure of 55/30 and a heart rate of 60 beats per minute. His cardiac rhythm on telemetry demonstrated multiple episodes of ventricular tachycardia. His condition and gravely poor prognosis was discussed with his family, and it was decided that the medical team would halt all attempts at cardiac resuscitation. The patient expired shortly after with his family at his bedside.

His family consented to an autopsy which revealed evidence of rheumatic heart disease, RV and LV dilatation and hypertrophy, and left atrial dilatation. His lungs had signs of acute and chronic passive congestion. Interestingly, there were histological signs of adenocarcinoma in his prostate. His final cause of death was determined to be due to pericardial and mediastinal hemorrhage status post open heart surgery for mitral and aortic valve replacement.

**References**


*Photograph courtesy of Esther Lee, MD*
A 55 YEAR-OLD MAN WITH MENTAL STATUS CHANGE AND SEVERE ANEMIA
Sugeet Jagpal, MD, and Anastasia Shnitser, MD

Case Presentation
A 55 year-old male with past medical history significant for mental retardation, a stage IV sacral decubitus ulcer, iron deficiency anemia and gastrointestinal bleeding presented from a long term care facility for acute onset of respiratory distress and change in mental status. On presentation the patient was found to have a GCS of three, and he was emergently intubated in the emergency department for airway protection. Following intubation his vital signs were stable.

Upon review of his recent lab work, it was noted that patient had hemoglobin (Hgb) of 6.4g/dL the day prior to admission with a known baseline of 8g/dL. A blood transfusion was ordered. However, the transfusion was delayed secondary to difficulties in cross matching the patient’s blood. His admission labs returned with a Hgb of 2.6g/dL, a stool guiac test was negative, and an elevated LDH as well as positive direct Coombs C3 complement and IgG were noted. The patient was transfused two units of O-blood while the blood bank worked to determine which antibodies the patient had and find a suitable match. Eventually, the patient was diagnosed with cold agglutinin autoimmune hemolytic anemia based on an increase in his cold agglutin IgM antibody titer. At that time, the options were to either delay further transfusion as it would potentially worsen the hemolysis or to transfuse warmed blood.

Shortly after admission the patient became febrile, hypotensive and tachycardic. Despite treatment with antibiotics and fluids, the patient lost his pulse and required cardiopulmonary resuscitation. Lab work during the code showed a Hgb of 2.7 g/dL, and the patient was given additional units of warmed blood. Unfortunately, the patient did not respond and expired within 24 hours of admission.

Discussion
Autoimmune hemolytic anemia (AIHA) is a disease in which antibodies bind to red blood cell surface antigens and initiate blood cell destruction. AIHA can be classified into warm and cold reactive antibody disease. With cold agglutinin AIHA, it is thought that the antibody binds to blood cells in the periphery (since blood cools as it passes through the smaller peripheral vessels), activating a complement cascade to the stage of C3b. C3b continues to adhere to the red blood cells (RBCs) while they are in circulation. The C3b-coated RBCs encounter receptor specific macrophages, which then engulf the RBCs and are cleared in the liver.

Cold agglutinin AIHA can range in severity from mild to life threatening, and febrile illnesses can exacerbate chronic mild hemolysis due to the elevation in complements as part of the acute phase reaction. Diagnosis of this anemia is made by measuring the cold agglutinin IgM antibody titers– the antibody titers measured at 4° C are greatly increased (up to 1:1 x 10^6) from a normal low titer of <1:16 at 4° C. Also, the thermal amplitude of the antibody is increased, and the antibody binds to the surface of RBCs at temperatures as high as 28° to 32° C, when the normal thermal amplitude of the antibody does not allow binding between 20 to 37° C.¹

Rapidly developing anemia with defects in tissue perfusion, such as in our patient, requires urgent treatment. However, treatment with blood transfusions can be difficult due to the ongoing hemolysis. Transfusion of warmed blood decreases the hemolysis because the antibody binding is impaired at warmer temperatures. Steroids are often given in conjunction with transfusions to blunt the patient’s immune response. Inducing hypothermia is sometimes part of the treatment in attempt to maximize tissue oxygen delivery.² Splenectomy, although mentioned in the literature, is usually not helpful since the macrophages are primarily cleared in the liver. There are also a few reports of successful treatment with monoclonal antibodies; however, they are not used for rapidly progressing hemolytic anemia.³

Patients with primary cold agglutinin disease usually have moderate anemia with occasional attacks of acrocyanosis when exposed to cold. These patients are generally elderly (70 to 80 years old) and have underlying malignancies. When a younger patient such as ours presents presents with acute onset of cold agglutinin disease, an infection with either Mycoplasma pneumoniae or infectious mononucleosis should be suspected. In these patients, additional treatment of the underlying disorder is helpful when anemia is not as rapidly progressive as in our patient.

References
A College Student with Fulminant Hepatic Failure

Christie Crawford, MD

Case Report
A 19-year-old female college student presented to her pediatrician’s office after experiencing three weeks of fatigue, abdominal pain, and nausea. At that time, the patient was diagnosed with a urinary tract infection and a viral illness and was given a prescription for Keflex. Over the next three days, the patient’s symptoms worsened, and she developed weakness, shortness of breath, and anorexia. She also noticed yellowing of her skin and darkening of her urine, which prompted her to go to the emergency department at an outside hospital. At the outside hospital, many laboratory results were abnormal and her clinical condition worsened. She was transferred to the intensive care unit at Thomas Jefferson University Hospital (TJUH) for further evaluation and treatment.

The patient had no significant past medical, surgical history, or family history. She took a multivitamin and an oral contraceptive daily and denied the use of any herbal supplements or over-the-counter medications. She had no known drug allergies. She reported social alcohol and marijuana use, most recently one month ago, and denied tobacco use. She denied recent sexual activity or foreign travel. Review of systems was positive for shortness of breath, nausea, vomiting, abdominal pain, decreased urine output, dark urine, muscle cramps, headache, dizziness, jaundice, anorexia, and a six-pound weight gain over three weeks.

Upon admission, the patient’s vital signs were within normal limits, and her physical exam was notable for jaundice, scleral icterus, diffuse abdominal tenderness and distension, ascites, and bilateral lower extremity pitting edema. Routine laboratories were notable for a white blood cell count of 51.9 B/L, a hemoglobin of 7.0 g/dL, and INR of 3.92, and creatinine of 2.5 mg/dL, a total bilirubin of 52.1 mg/dL, a direct bilirubin of 21.8 mg/dL, and alkaline phosphatase of less than 5 IU/L, a lactate dehydrogenase of 963 IU/L, a haptoglobin of less than 6 mg/dL, and a lactate of 28.4 mg/dL.

Hospital course
With all clinical and laboratory findings pointing towards fulminant hepatic failure, a search for the cause was initiated. Tests for hepatitis B, hepatitis C, HIV, EBV, CMV, parvovirus, syphilis, SLE, autoimmune hepatitis, and acetaminophen-induced liver toxicity were all negative. The suspicion for Wilson Disease was high, but ceruloplasmin, urine and serum copper levels were still pending. Over the first two days of the patient’s hospitalization, her condition worsened, and it became clear that she would require a liver transplant for survival. The patient was listed as status one for orthotopic liver transplantation with the presumptive diagnosis of Wilson Disease.

On the third day of hospitalization at TJUH, the patient began to get more confused and somnolent. The patient also became anuric with severe and progressive renal failure, requiring hemodialysis. The patient developed respiratory distress and was intubated. Additionally, she became hypotensive, and pressors were initiated. The patient was now severely acidic, had a lactate of 197.7 mg/dL, an INR of 6.77 with diffuse bleeding, and one of her pupils was fixed and dilated. The patient was taken to the operating room for hepatectomy, despite the fact that the donor liver transplant had not yet arrived at TJUH. Two hours later, the donor liver arrived and the patient underwent transplantation.

After the transplant was completed, the patient improved clinically, and her laboratory values also began to return towards normal. Her neurologic and cognitive function returned to baseline. She required one return trip to the operating room for bile duct reconstruction and was discharged from the hospital on post-operative day 19. The final diagnosis of Wilson Disease was made post-operatively when the patient’s serum copper came back at 270 mcg/dL (normal range: 80-155), and her urine copper came back at 2371.4 mcg/dL (normal range: 0.2-8). Ceruloplasmin was within normal limits.

Discussion
Wilson Disease, also known as hepatolenticular degeneration, is an autosomal recessive disorder caused by mutations in the ATP7B gene, which codes for a membrane-bound copper-transporting ATPase. When functioning properly, this ATPase transports copper into the bile so that it can be excreted from the body via the gastrointestinal tract. In patients with Wilson disease, copper cannot be excreted into the bile and thus accumulates in the liver bound to a protein called metallothionein. Mutations in the ATP7B gene also impair the incorporation of copper into ceruloplasmin. Excess copper in the liver causes increased generation of free radicals, which lead to liver damage. This progressive liver damage eventually leads to cirrhosis. A cirrhotic liver is unable to maintain the huge amount of accumulated copper, so the copper begins to leak into the bloodstream where it accumulates in and damages other tissues.1

Wilson Disease affects one in 30,000 live births. Symptoms rarely occur before age six and are almost always present by age thirty, with a mean age of onset of sixteen. Two times more females with Wilson Disease progress to fulminant hepatic failure than do their male counterparts.1,2

Neurologic symptoms, such as Parkinsonism, dystonia, cerebellar dysfunction, or pyramidal signs are the presenting features of Wilson Disease in 69% of patients. These neurologic manifestations result from accumulation of copper in the basal ganglia. Neurologic symptoms are often associated with psychiatric symptoms such as anxiety, depression, and psychosis, but psychiatric symptoms are rarely seen in the absence of neurologic symptoms. Approximately 15% of patients with Wilson Disease...
present with signs and symptoms of cirrhosis, while another 5% have asymptomatic liver function test abnormalities. It is much less common for patients to present with isolated musculoskeletal complaints such as premature osteoporosis or osteoarthritis. It is also uncommon for patients to present with fulminant hepatic failure, as the patient in this case did.²

Kayser-Fleischer rings are brownish-gray rings seen around the iris that consist of copper deposits in Descemet’s membrane that are commonly seen in Wilson Disease. They can only be appreciated on a slit lamp exam and are present in greater than 90% of Wilson Disease patients with neurologic and psychiatric symptoms. In patients with Wilson Disease without neurologic or psychiatric symptoms, Kayser-Fleischer rings will only be present 50% to 60% of the time.³

The patient in this case presented with fulminant hepatic failure which is unusual for Wilson Disease. Clinicians must have a high index of suspicion in order to make this diagnosis. Children and young adults who present with liver failure and also have a Coombs negative hemolytic anemia, a coagulopathy that is unresponsive to vitamin K, renal failure, mild AST and ALT elevations, and/or alkaline phosphatase levels of less than 40 IU/L should be considered to have Wilson Disease until proven otherwise, as this presentation is associated with a very high mortality rate if not treated appropriately and in a timely fashion.⁴

The gold standard for diagnosing Wilson Disease is a liver biopsy with quantitative copper assay. However, this is rarely the first step in making the diagnosis. Patients with suspected Wilson Disease must first have liver function tests including coagulation studies, a complete blood count, a ceruloplasmin level, a 24-hour urine copper assay, and a thorough physical exam including a slit lamp exam. Patients with Kayser-Fleischer rings, a decreased serum ceruloplasmin, or urine copper levels greater than 40 mcg/day need a liver biopsy to confirm the diagnosis. Copper levels of greater than 250 mcg/g on liver biopsy are consistent with a diagnosis of Wilson Disease. The work-up and diagnosis of Wilson Disease is a lengthy process and in patients with fulminant hepatic failure like the one in this case, treatment must be initiated before a diagnosis is finalized in order to give the patient the greatest chance of survival.³,⁴

Treatment of patients with Wilson Disease depends on whether or not the patient is symptomatic. Asymptomatic patients diagnosed via screening tests should be treated with the copper chelating agent penicillamine or with zinc, to remove copper that has already accumulated in the liver and prevent the further accumulation. For symptomatic patients, the copper chelating agent trientine should be used until laboratory tests confirm that copper levels have returned to the normal range, at which point patients may be switched to maintenance therapy with penicillamine or zinc. Patients with Wilson Disease must remain on copper chelation therapy for life, for if is stopped, copper will begin to reaccumulate. For patients that present with fulminant hepatic failure, emergent liver transplant is the only treatment available, and it is curative.⁴

Wilson Disease has an excellent prognosis if diagnosed and treated early. Neurologic and hepatic symptoms resolve with appropriate treatment. It is unclear as to whether there is an increased risk of hepatocellular carcinoma in patients with Wilson Disease.⁵ Prognosis for patients who present with fulminant hepatic failure is poor and depends on the availability of liver transplantation.

As Wilson Disease is a genetic disorder, screening of siblings and children of patients with the disease is necessary. Possible patients should be screened with slit-lamp examination, liver function tests, serum ceruloplasmin and copper levels, and 24-hour urine copper excretion. If any of these tests are abnormal, a liver biopsy should be done to confirm the diagnosis. Occasionally, genetic testing may be performed, if the specific mutation of the ATP7B gene in the proband is known. When a patient’s screening test for Wilson Disease is positive, treatment should be started immediately to ensure the best possible outcome.

References
A Case of Drug-induced Hepatotoxicity: Amiodarone is Not Always to Blame

Brendan O’Hare, MD

Case Presentation
A 54 year-old male presented to the hospital with a two week history of new onset jaundice, anorexia and fatigue. The patient has a past medical history of hypertension, coronary artery disease, and ischemic cardiomyopathy with an ejection fraction of 10% to 15%. He also has a history of atrial fibrillation and paroxysmal ventricular tachycardia with an automated implantable cardioverter-defibrillator placed. He denied any history of blood transfusions, alcohol use, intravenous drug abuse, or known hepatitis. He also denied taking herbal medications or vitamins. The patient denied fevers, night sweats, nausea, shortness of breath, abdominal pain, blood in his stool, or easy bruising. Four weeks prior to admission, the patient was diagnosed with hyperthyroidism thought to be secondary to long-term amiodarone use which the patient had been taking for eight years for treatment of atrial fibrillation. At that time he was started on 10 mg of methimazole daily, and his amiodarone was stopped. All of his other medications were chronic and include atenolol, pantoprazole, aspirin, clopidogrel, and furosemide. He has no known drug allergies. Upon admission his methimazole was stopped since his symptoms could be attributable to this medication.

On presentation the patient was afebrile. His pulse was regular at 112 beats/minute, and his blood pressure was 91/61 mm Hg. He was orientated to person, place, and time. His exam was noteworthy for scleral icterus and jaundice. There was no ascites, asterixis, palmer erythema, spider angiomata or other evidence of liver disease. His abdominal exam was benign, with no tenderness to palpation, organomegaly, or lymphadenopathy. He did have 2+ lower extremity swelling that was thought to be chronic and secondary to his heart disease.

Laboratory results are shown in Table 1. All other laboratory values were within the reference range. An EKG did not show any acute changes, and three consecutive troponins were negative. An abdominal ultrasound was notable for the presence of hepatosplenomegaly with the liver measuring 14.4 cm in sagittal length and the spleen measuring 14.4 cm. Color doppler ultrasound showed patent portal, hepatic, and splenic veins. There was no biliary ductal dilation, cholelithiasis or sludge.

On hospital day two the patient’s clinical status had not improved, and a liver biopsy was obtained to help differentiate the cause of hepatic dysfunction. The liver biopsy (Figure 1) showed severe cholestasis with mild inflammatory changes and mallory bodies on pathology. Given the time course of introduction to methimazole and the development of abnormal liver tests, the presumptive diagnosis of methimazole-induced hepatotoxicity was made. The patient experienced a relatively stable course until day six of his stay. At that time the patient became clinically unstable, went into cardiac arrest and died. It was presumed that the new onset liver failure proved to be too much of a stressor on an already weak heart.

Discussion
Methimazole and its precursor molecule carbimazole are common treatment options for hyperthyroidism but do not come without significant risk to the patient: methimazole is a known hepatotoxin. An extensive review of the literature has not identified any previous case reports of methimazole-induced liver injury leading to death in the United States. There

<table>
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<th>Chem 7</th>
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<td>Triiodothyronine 3.63</td>
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Table 1. Laboratory values at presentation.
was a case report of necrotizing hepatitis leading to death in Germany. There have been case reports associating fulminant hepatic failure and death with the antithyroid agent propylthiouracil in the United States. However, up to this point methimazole liver injury has not been associated with any deaths in the United States.

There were many diagnoses in the differential that were sequentially ruled out during this patient’s admission, including chronic viral hepatitis, biliary and portal vein thrombosis, infiltrative and chronic passive congestion, and ischemic liver injury. One drug considered in addition to methimazole for causing hepatotoxicity in this patient was amiodarone. It was difficult to apply the established scoring systems for assessing causality between a drug and hepatocellular injury in this case because the patient expired before rechallenge of the potential offending agent was possible. However, considering the temporality of the treatment, it is likely that methimazole and not amiodarone was the cause of liver injury. The patient had been stable on amiodarone for eight years without any noted hepatotoxicity. In contrast, methimazole had been started four weeks prior to development of jaundice. The aforementioned scoring systems for deducing the cause of drug-induced liver injury put a much greater weight on drugs that cause injury in a window of roughly five days to three months. The patient’s amiodarone use did not fall into this time interval. In fact, the median time for liver disease associated with amiodarone is 21 months after initiation.

The liver biopsy was also not consistent with amiodarone-induced liver injury. Changes in pathology that are usually associated with amiodarone drug toxicity include Mallory’s hyaline, steatosis, ballooning of hepatocytes, focal necrosis, fibrosis, and in severe cases, cirrhosis. Although our patient did have Mallory bodies on specimen, none of the other defining characteristics of amiodarone toxicity were present. As mentioned, the biopsy showed diffuse cholestasis with intracanalicular bile plugging (Figure 1). As of 1999 there had only been seven case reports published of jaundice and cholestasis presenting as the major clinical and pathological manifestations of amiodarone induced hepatotoxicity. Conversely, the majority of methimazole liver injury cases have reported cholestasis and associated jaundice.

This case serves as an example of a serious but uncommon drug related liver injury. Generally, patients with severe liver injury, as defined by serum ALT being three times the upper limit of normal or the serum bilirubin being two times the upper limit of normal in the absence of biliary obstruction, have a mortality of at least 10%. In our case the patient had a bilirubin that was over 20 times normal levels. Additionally, our patient had two of the three hallmarks of acute liver failure: jaundice and impaired hepatic synthetic function. During the course of his admission he did not develop the third characteristic which is encephalopathy. If the full triad of manifestations is present in cases of drug induced hepatotoxicity, patients have roughly a 25% survival rate without liver transplant. However, prognosis also depends on agent as there is a 0% mortality of erythromycin induced liver failure versus 40% mortality with use of halothane.

It is of crucial importance to recognize drug induced liver toxicity because it is now the leading cause of acute liver failure among patients referred for liver transplantation in the United States. Hepatotoxicity related specifically to antithyroid agents occurs with an approximate frequency of 0.1% to 0.2%. It is plausible, however, that this number may be falsely low secondary to difficulty in diagnosis and underreporting.

In this case, the patient’s co-morbidities allowed for close physician follow up and an apparent drug induced liver injury was caught just four weeks after the inciting agent was started. However, not all patients will be followed so vigilantly after starting potentially hepatotoxic drugs. It is important for the responsible physician to be aware of potential liver injury that drugs such as methimazole may cause in order to prevent their rare but unfortunate complications.

![Figure 1. Liver biopsy shows diffuse cholestasis, mallory bodies, and intracanalicular bile plugging. There were no viral inclusion bodies, steatosis, necrosis, or fibrosis.](image)

**References**


A Woman With Chest Pain, Syncope, and Transaminitis
Ankitkumar K. Patel, MD, MPH, and Brendan O’Hare, MD

Case Presentation
The patient is a 49 year-old female with past medical history of anxiety and hyperlipidemia who presented to an outside hospital with complaints of five hours of substernal chest pain followed by three episodes of syncope witnessed by her son. At presentation in the emergency department the patient denied any current chest pain or shortness of breath. She received 325 mg of aspirin en route to the hospital by EMS. Her vital signs were temperature 100° Fahrenheit, heart rate 60 beats/minute, blood pressure 101/50 mm Hg, respiratory rate 20 breaths/minute, and a pulse oxygenation of 98% on room air. The patient’s EKG showed ST elevations in the inferior leads. The patient’s laboratory studies were: wbc 14 B/L, hemoglobin 13.2 g/dL, platelets 153 B/L, CKMB 32 U/L, troponin 8.27 ug/L, and CK 24.5 U/L. The patient was started on intravenous heparin and integillin drips and transferred to Jefferson for emergent cardiac catheterization.

The patient had left and right coronary angiography which showed no evidence of occlusive coronary disease. Left heart catheterization demonstrated moderate to severe infarct related hypokinesis and a mildly depressed left ventricular ejection fraction (40%). During the procedure, the patient was noted to have 2:1 AV heart block with intraventricular conduction delay, and a temporary transvenous pacemaker was placed. The patient was then transferred to the cardiac care unit.

In the cardiac care unit, the patient reported that she had no known drug allergies. Her only outpatient medication was a statin that was started six weeks ago. The patient denied any past surgical history. The patient consumed alcohol socially, had a 15 pack year history of smoking, and no history of illicit drug use. The patient’s father died of a myocardial infarction at age 62, and the patient’s mother was alive with a history of diabetes mellitus and arrhythmia. The patient noted that she had some nasal congestion for two days prior to the chest pain and syncope. The patient also reported working in her garden with rose bushes and was certain that she had a neck rash due to poison oak. Lastly, the patient reported decreased oral intake for the past two days due to “flu-like” disease.

Overnight, the patient had multiple episodes of bradycardia that warranted venous pacing on telemetry. Significant laboratory studies were: wbc 4.3 B/L, AST 539 U/L, ALT 313 U/L, and troponin 14.7 ug/L. The patient underwent successful implantation of a dual chamber VDD pacemaker. A transthoracic echocardiogram demonstrated an ejection fraction of 40%, moderate mitral regurgitation, and an inferior vena cava normal in size without inspiratory collapse. The patient was transferred to the telemetry floor service.

On the third hospital day, the patient had no overnight complaints and wanted to be discharged home. Significant laboratory studies were a troponin of 16.5 and AST 299 U/L, and ALT 250 U/L. The patient had a CT of her head which showed no fracture or bleed. A CT of her chest demonstrated multifocal pneumonia with bilateral pleural effusions and subcentimeter pulmonary nodules. The patient was diagnosed with pneumonia and was started on ceftriaxone, azithromycin and flagyl.

On the fourth hospital day, the patient had an overnight fever of 100.7° Fahrenheit and an episode of oxygen desaturation to 89% on 2 liters oxygen via nasal cannula. Significant laboratory studies were: wbc 14.9 B/L, troponin 14.1 ug/L, AST 247 U/L, and ALT 240 U/L.

On the morning of the fifth hospital day, the patient had a fever of 100.6° Fahrenheit and an episode of tachycardia with oxygen desaturation to 75% on 2 liters with an increased respiratory rate (18 to 28 breaths/minute). An arterial blood gas showed pH 7.50, pCO2 23, PO2 138, HCO3 18, O2 sat 99%. Significant laboratory studies were wbc 18.9 B/L, troponin 8.9 ug/L, AST 279 U/L, ALT 288 U/L, lactate 40.8 mmol/L, and BNP 2058. The patient was treated with nebulizer treatments, intravenous furosemide, and an anxiolytic. A transthoracic echocardiogram demonstrated an ejection fraction of 25%, moderate-severe mitral regurgitation, severely decreased left ventricular systolic function with segmental wall motion abnormalities, mild right atrial enlargement, dilated inferior vena cava, and right ventricular enlargement with decreased function.

Later in the afternoon, the patient had complaints of shortness of breath and increased anxiety. Vital signs at the time were heart rate 123 bpm, blood pressure 100/60 mm Hg, respiratory rate 36 breaths/minute, pulse oxygenation of 90% on 100% non-rebreather mask. An arterial blood gas demonstrated pH 7.49, pCO2 27, PO2 60, HCO3 20, O2 sat 93%. The patient was once again treated with nebulizer treatments, intravenous lasix and had symptomatic relief. Three hours later, the patient had worsening respiratory distress and was found to have a respiratory rate of 48-60 with a pulse oxygenation of 68% on room air and 88% on 100% non-rebreather mask. A rapid response was called for worsening respiratory distress.

The patient was transferred to the cardiac care unit and emergently intubated. Subsequently, the patient became progressively hypotensive and a central line was placed, and intravenous norepinephrine was started. The patient was presumed to have worsening sepsis secondary to multifocal pneumonia with cardiomyopathy of sepsis. Antibiotic coverage was broadened to vancomycin and zosyn. In addition, doxycycline was added to cover possible rickettsial infections. A complete rheumatologic and autoimmune work up was sent for laboratory studies.

The following day, the patient had a transesophageal echocardiogram which showed no vegetations. Azithromycin was added to cover atypical organisms, and the patient was started...
on an acute respiratory distress syndrome ventilator protocol. Significant laboratory studies were: wbc 23.1/B/L with 6% bands, AST 1209 U/L, ALT 873 U/L, and troponin 6.29 ug/L.

On the seventh day, the patient underwent fiberoptic bronchoscopy which was grossly normal and bronchoalveolar lavage of the right upper lobe was sent for cultures. Significant laboratory studies were: wbc 19.1 U/L, creatinine 1.5 umol/L, AST 2220 U/L, and ALT 1516 U/L. The patient became progressively more hypotensive, and the norepinephrine drip was titrated. The patient also had decreasing urine output and worsening transaminits was thought to be due to ischemic hepatitis.

On the eighth day, the patient developed a supraventricular tachycardia which was treated with adenosine and revealed an underlying atrial flutter rhythm. The patient was started on digoxin for rate control. With worsening hypotension and tachycardia, the patient was started on phenylephrine with plans to wean down norepinephrine. Due to worsening clinical status, Xigris therapy was also initiated. A transthoracic echocardiogram showed an ejection fraction of 10%, moderate-severe mitral regurgitation, severe left ventricular systolic function (with only the basal-inferolateral segment contracting – the remainder was hypokinetic/akinetic), right ventricular enlargement, moderate-severe tricuspid regurgitation. Late in the evening, the patient’s clinical exam had a significant change with cool extremities and hypothermia. Laboratory studies were consistent with a state of disseminated intravascular coagulation and worsening renal function. A family meeting was called to discuss the worsening clinical status and overall prognosis.

Cardiology consultation offered right heart catheterization and the placement of an intraortic balloon pump (IABP). The right heart catheterization showed HR 130, aortic pressure 91/59, PA 55/39 mean 45, wedge 54, RA 50/49 mean 40, RV 55/39, SVR 750, PVR 1126, CO by Fick 3.20, CI by Fick 1.59. The patient was diagnosed with cardiogenic shock, and the IABP was set at 1:1 and a Shiley catheter was placed for urgent continuous hemodialysis. The patient was weaned off of the phenylephrine and started on dobutamine, dopamine, and eventually epinephrine.

On the morning of the ninth hospital day, the cardiac care unit, heart failure, pulmonary, renal, and cardiothoracic surgery teams discussed the patient’s case. Significant laboratory studies were: wbc 21 U/L, hemoglobin 7.9 g/dL, platelets 59 B/L, creatinine 2.5 umol/L, and AST 12217 U/L, and ALT 4060 U/L. Due to the rapid and progressive decline in cardiac function due to severe myocarditis, a decision was made to place a right ventricular assist device (RVAD) and a left ventricular assist device (LVAD), commonly called a BiVAD. The patient underwent surgery with the RVAD connecting the right atrium to the pulmonary arteries and the LVAD connecting the left ventricle to the aorta. A cardiac myocardial biopsy was also conducted during the surgical procedure. A collection of all lab results is included in Table 1.

Discussion

Often, myocarditis is an under-diagnosed medical condition. Its pathophysiology is marked by a triad: cardiac injury by inciting agent, immunologic response, and inflammation. Generally speaking 1/3 of patients recover, 1/3 experience permanent cardiac dysfunction, and 1/3 deteriorate to either death or cardiac transplant.

Myocarditis’ true incidence is most likely under represented. It has been postulated that up to 8.6% of sudden cardiac deaths may be attributable to myocarditis. Up to 10% to 40% of what was thought to be idiopathic dilated cardiomyopathy in children may in fact be occult myocarditis. As diagnostic techniques such as immuno-histochemistry, electron microscopy, and molecular proteomics advance inevitably the incidence of myocarditis will rise.

The diagnosis most often implies viral infection. The most common vectors of disease have thought to be enteroviruses such as coxsackie or adenovirus. However, any virus can cause myocarditis: cytomegalovirus, parvovirus, influenza, human immunodeficiency virus, hepatitis C, and Epstein-Barr virus have all been implicated. Furthermore, tricyclic antidepressants, clozapine, the smallpox vaccine, radiation, heat stroke, and hypothermia can all cause inflammation of cardiac tissue.

Clinically, the onset of symptoms can be insidious or rapid. Acutely, a viral prodrome often predominates with signs including fatigue, arthralgias, and fever. After this, cardiac manifestations may develop. In this particular case our patient presented with arrhythmia and heart block, which can be seen as the presenting symptom in 5% of cases. Other symptoms such as chest pain and heart failure are often also present. Unfortunately, some patients may present with hemodynamic compromise and a fulminating picture.

Laboratory testing can include elevated ESR, WBC, or troponin. EKG findings are often non-specific and may range from subtle abnormalities to ST elevations. One study revealed that in the setting of an acute myocardial infarction and normal cardiac catheterization, 38% of patients were thought to have myocarditis. Non-invasive techniques include transthoracic echocardiography in which regional wall motion abnormalities are typically more common than cardiac dilation. This is especially true in the acute to sub-acute period before cardiac remodeling has occurred. A less common used modality is indium-111 anti-myo-sin imaging. This is a nuclear medicine study in which anti-myosin antibodies are introduced, they bind to injured myocardium, and the results can then be quantified. The technique is excellent for detecting damage; however, distinguishing between a myocardial infarction and myocarditis may be difficult. In fact, the sensitivity is good at 85% to 100%, but the specificity is only 55%.

Another option
is cardiac MRI which uses contrast kinetics to identify areas of damage and may be able to differentiate myocardial infarction from myocarditis. Epicardial predominance, a non-contiguous pattern, and involvement of the lateral wall are more common in myocarditis according to one study.6

The gold standard in the diagnosis of myocarditis is biopsy. For 20 years, the Dallas criteria have defined a positive biopsy as one that displays inflammatory cells plus necrosis. A borderline biopsy is one that has inflammatory cells but no necrosis.7 However, this system is imperfect. The nature of myocarditis is such that it does not involve the entire myocardium. As such, even if one takes five biopsy specimens, the diagnosis will be missed 33% of the time.8 Moreover, the disease often affects the lateral wall which is difficult to biopsy using current techniques. Detection of myocarditis via pathology can also be subject to observer differences. Furthermore, there are risks involved with the procedure such as vascular access issues, arrhythmias, and perforation.

Prognosis generally depends on the type of myocarditis. For example, giant cell myocarditis usually progresses quite rapidly, while other forms progress more subtly. As stated previously, patients may recover completely, sub-acutely progress to permanent cardiac dysfunction, or rapidly deteriorate to death or transplant. Generally, there is a 20% mortality at one year and 50% at four years. Predictors of death or requiring transplantation in the future include the presenting symptom of syncope or bundle branch block, an ejection fraction of <40%, and persistence of viral genome in the myocardium.9 Unfortunately, our patient had two of these three predictors.

Regrettably, the treatment options for myocarditis leave much to be desired. The first steps are supportive therapies such as ACE inhibitors, diuretics, and beta blockers when clinically stable. The National Institutes of Health conducted a trial in which they randomized standard heart failure therapy versus steroids + azathioprine versus steroids + cyclosporine for six months. The results showed no difference in ejection fraction or mortality after four years.10 There was some improvement during the acute treatment phase, but this was transient. Final recommendations included considering steroids in giant cell myocarditis or in hemodynamic compromise. In another trial,

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Case Reports

Table 1. Laboratory results

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interferon was used to treat 22 patients for six months. Virus was eliminated from myocardium in all 22 patients and 15 of 22 showed improvement in left ventricular systolic function. The results were fairly promising and, consequently, have spurred an ongoing phase III trial. IVIG has been sought as therapy due to its effects on auto-antibodies. In 2003, IVIG was compared to placebo. Systolic function improved from 25% at baseline to 41% at six months, but there was no statistical difference in the two arms of the trial. Currently, the most recognized treatments are supportive. Specifically, left ventricular assist devices have been shown to be beneficial in select patients. Indications for LVAD include: cardiac index < 2.0L/min/m2, central venous pressure or left atrial pressure >20, and urine output <20mL/hour despite maximal pharmacological therapy. Furthermore, the disease may be so progressive that both right and left ventricular assist devices may be needed, such as in this case presented here. Indications for a BiVAD are renal, hepatic, and pulmonary dysfunction, seen with our patient.

References
VITAMINS: FRIEND OR FOE
Anastasia Shnitser, MD, and Dina Halegoua-De Marzio, MD

Case Presentation
A 39 year-old male presented to the emergency department with generalized body aches after a recent fall. The patient underwent urgent trauma evaluation and incidentally was found to have multiple medications in his right colon on radiography (Figures 1 and 2). The patient was immediately screened for a drug overdose, but he admitted to taking a large amount of Ultra-Start vitamins that he purchased on the internet. Due to suspicion for possible drug overdose, a nasogastric tube was placed, and polyethylene glycol was administered to help the patient pass the pills from his bowels. Despite the large ingestion of vitamins, the patient remained asymptomatic throughout his hospitalization.

Discussion
The ability to visualize medications in the gastrointestinal system on imaging depends on the radiodensity of the ingested material. Chloral hydrate, iron-containing preparations, calcium carbonate, iodinated compounds, acetazolamide, busulfan, and potassium-containing preparations are consistently radiopaque.1,2 The Ultra-Start vitamins ingested by our patient contained multiple radiodense compounds including iron and calcium carbonate.

There is minimal regulation of the content of nutritional supplements, so patients purchasing vitamins often do not know what they are getting. Some formulations will have extremely poor absorption. Some of the lowest grade nutrients include magnesium oxide, calcium carbonate, vitamins B12, B6, C and D.3 The patient in our case was taking vitamins that contained several poorly absorbed combinations.

It is not only important for patients to take the correct vitamin supplementation, but it is important for providers to understand that actual vitamin and mineral amounts often deviate from label values. Potentially toxic levels of vitamins can be achieved easily in people who take high potency vitamins or a large number of pills.

References

Figure 1. Lumbar X-ray on admission shows the presence of multiple radiopaque pills in the right colon, representing the patient's ingestion of Ultra-Start vitamins.

Figure 2. Abdominal CT scan on admission similarly demonstrates that the right colon contains many radiopaque vitamin tablets.
A CASE OF SEVERE ANEMIA IN AN AIDS PATIENT
Amy K. Slenker, MD, and Rahul Anand, MD

Case Presentation
A 49 year-old African-American male presented to Thomas Jefferson University Hospital in April of 2008 complaining of generalized weakness and lightheadedness for 4 months. The patient had a medical history of HIV/AIDS diagnosed in 2002 with a CD4 count of 0 cells/mm³ in 2005 and a history of non-compliance with highly active retroviral therapy (HAART). In December of 2007 the patient was diagnosed with cryptococcal meningitis and had a concomitant anemia with a hemoglobin of 5.3 g/dL. At that time laboratory studies for parvovirus B19 (PB19) showed an IgG of 0.79 units and an IgM of 0.63 units (a value less than 0.89 is considered negative). PB19 DNA by PCR or direct DNA hybridization was not checked at that time. A bone marrow biopsy was performed in January of 2008 to determine the etiology of this severe hypoproliferative anemia, revealing hypercellular marrow containing maturing trilineage hematopoiesis with occasional non-caseating granulomas with fungal elements. It was felt at this time that the anemia was secondary to cryptococcal invasion of the bone marrow. The patient was treated for cryptococcal meningitis with fluorocytosine and liposomal amphotericin B for 2 weeks, followed by oral fluconazole indefinitely, and was discharged from the hospital.

When the patient presented in April of 2008, he was admitted through the emergency department (ED) for a work-up of symptomatic anemia. The patient was complaining of lightheadedness, generalized weakness, watery diarrhea, dry cough, and shortness of breath. The patient denied fever, night sweats, headache, blurry vision, joint pains, or rash. The patient denied bloody or tarry stools, bleeding gums, easy bruising, or trauma. On exam, the patient was afebrile and appeared disheveled and cachectic with marked pallor. The patient had multiple small cervical lymph nodes, no evidence of jugular venous distension, and was clear to auscultation on lung exam. He had a regular cardiac rhythm with no murmurs, a benign abdominal exam with no hepatosplenomegaly, and no rashes, petechiae, or peripheral edema.

The patient’s hemoglobin in the emergency room was 2.9 g/dL, with a previous level of 13.1 g/dL one year prior to this admission. The patient’s WBC count was 8.2 g/dL, with a differential of 24% neutrophils, 9% bands, 23% lymphocytes, 28% monocytes, and 3% eosinophils, 3% metamyelocytes, and 9% myelocytes. Laboratory values were as follows: mean corpuscular volume was 87 fl (80-99 fl), lactate dehydrogenase 285 IU/L (100-200 IU/L), haptoglobin 331 mg/dL (16-200 mg/dL), urea-nitrogen 15 mg/dL, creatinine 1.7 mg/dL, aspartate aminotransferase 16 IU/L, alanine aminotransferase 11 IU/L, alkaline phosphatase 103 IU/L, albumin 3.6 g/dL, total bilirubin 0.3 mg/dL, and direct bilirubin 0.0 mg/dL. CMV quantitative PCR was <100 copies/mL (<100 copies/ml is negative). AFB stain from feces and blood cultures were negative. Stool studies were negative for Entamoeba histolytica, Giardia lamblia, Cryptosporidium species, Clostridium difficile and Shigella, Salmonella, and Campylobacter species. The patient’s absolute reticulocyte count was 3 cells/mm³ (20-76 cells/mm³), HIV viral load was 483,000 copies/mL and CD4 count was 7 cells/mm³. PB19 DNA by PCR was positive, and there was a positive antibody response with an IgG of 1.56 index units and IgM of 4.84 index units.

The patient received four units of packed red blood cells in the ED and was subsequently started on intravenous immune globulin (IVIG), to which he responded with a sustained increase in his hemoglobin and no further requirements of packed red blood cell transfusions. The patient’s acute renal failure was felt to be secondary to pre-renal causes and improved to a baseline value with fluid resuscitation. The patient was also started on HAART with Atazanavir boosted with Ritonavir, and Tenofovir-Empiricitabine. The patient’s hemoglobin on discharge was 9.3 g/dL with an absolute reticulocyte count of 198 cells/mm³. On follow up, he continues to be non-compliant with his HAART medications, but his repeat complete blood count three months later in August 2008 revealed a hemoglobin of 9.0 g/dL. Furthermore, the patient has not required a blood transfusion since he completed IVIG treatment.

Discussion
Anemia is a common finding in HIV-infected patients. Several causes of anemia have been described including medications (e.g., antiretrovirals or trimethoprim-sulfamethoxazole), neoplasms, opportunistic infections, and the immunological effects of HIV itself. Although uncommon, PB19-related pure red cell aplasia (PRCA) is an important diagnosis to consider in this setting because it is a treatable cause of anemia. PB19 infection is found worldwide in persons of all ages, with the majority of adults having been exposed to the virus by age 50. The virus can be asymptomatic or can present in a variety of ways including as erythema infectiosum, arthropathy, a papular rash, pure red cell aplasia, hydrops fetalis in the neonate, and other cardiac, rheumatologic, and neurological manifestations.

PB19 usually causes a benign, self-limited illness, but the virus can present as a severe anemia in the immunocompromised host.

**Figure 1.** Characteristic giant proerythroblasts in the bone marrow are pathognomonic for parvovirus B19 infection. The diagnosis may be missed if the biopsy is done within a few days of a blood transfusion.
HIV-infected patients are particularly susceptible to infection with PB19 and may be unable to produce an adequate antibody response to the virus. This can result in a severe PRCA and a prolonged anemia as the PB19 interrupts the production of red blood cells in the bone marrow.5,6 These patients have been shown to respond to a PB19 triggered PRCA with both IVIG therapy as well as with highly active antiretroviral therapy.7,10 In this case report, our patient presented with a profound anemia caused by parvovirus B19 and responded well to treatment with IVIG. The patient was also started on HAART, but was again non-compliant with his medications.

A diagnosis of B19-PRCA should be considered in an afebrile, HIV-infected patient with a normocytic anemia of relatively recent onset, a virtual absence of blood reticulocytes, and a normal renal function. Most reported cases are with a CD4 count less than 100 cells/mm3.7,12 The symptomatology is nonspecific, and fever, skin rash, and arthropathy are characteristically absent. Diagnosis of PB19-induced PRCA in an HIV-infected patient is established when the following criteria are met: a bone marrow aspirate consistent with PB19, a positive serum PB19 IgM and IgG antibodies to PB19 is not sufficient to exclude the infection. It is important to note that the diagnosis may be missed in immunocompromised patients because these patients may not be able to formulate antibodies to the virus. Therefore, only checking IgM and IgG antibodies to PB19 is not sufficient to exclude the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4 There are no clinical guidelines about the diagnosis, and either DNA by PCR or direct DNA hybridization must be ordered.4
MAN WITH SWOLLEN EYE, BLURRED VISION, AND FEVERS IN THE SETTING OF NEWLY DIAGNOSED MDS

Rory Bowers, MD

Case Presentation
An 82 year-old male with a past medical history of prostate cancer, atrial fibrillation, gout, and recently diagnosed myelodysplastic syndrome presented with a chief complaint of left eye pain. The patient also reported peri-orbital numbness, swelling, and clear discharge as well as episodic blurry vision of his left eye. Over the previous two months he had been admitted to the hospital multiple times complaining of cough and high fevers and was subsequently treated with several courses of antibiotics for presumed pneumonia. During the initial admission for pneumonia he was noted to have a relative pancytopenia. A bone marrow biopsy was eventually undertaken revealing a diagnosis of myelodysplastic syndrome (MDS).

Prior to the current presentation, his facial numbness, erythema, and peri-orbital swelling had persisted over the period of three weeks. He was seen in an outpatient clinic, diagnosed with a peri-orbital cellulitis, and treated with a course of oral clindamycin, levofloxacin, and erythromycin eye drops. During his last outpatient follow up he was told to go directly to the emergency room secondary to the worsening appearance of his left eye. On current presentation he denied any fevers, chills, or sweats. He denied traumatic injury to his eye. He also denied headaches or other neurological complaints but occasionally experienced blurred vision in his left eye, which usually resolved spontaneously. He had significant pain around his left eye, which was worse with eye movements. He denied photophobia and noted that his symptoms had not improved over the past three weeks. In addition, he had continuous feelings of numbness across his left face. He denied sore throat, chest pain, recent weight loss, myalgias, or arthralgias. His cough had persisted since his diagnosis of pneumonia and was non-productive in nature.

His current medications were aspirin, erythromycin eye drops, levofloxacin, furosemide, digoxin, potassium chloride, metoprolol, clindamycin, and percocet. He had an allergy to penicillin, which had caused a rash in the past. He denied alcohol, tobacco, or substance abuse. A family history was notable for coronary artery disease and asthma.

On physical exam his vitals were noted to be the following: temperature 97.6° Fahrenheit, respiratory rate 20 breaths/minute, heart rate 87 beats/minute, blood pressure 160/90 mm Hg, and pulse oximetry of 95% on room air. He was noted to have prominent left periorbital swelling and erythema with a moderate amount of clear discharge. He had mild periorbital tenderness and his left sclera appeared injected. The pupils remained reactive to light and accommodation and his extra-ocular movements were intact. The visual acuity in the left eye was moderately reduced. His cardiac exam revealed only an irregularly irregular rhythm consistent with known atrial fibrillation. His lungs had mildly decreased breath sounds at the right base but were otherwise clear. His abdomen was benign. He was neurologically intact with the exception of left facial numbness. He had mild lower extremity pitting edema bilaterally.

Laboratory tests revealed a mild pancytopenia: white blood cell count 3.6 B/L, hemoglobin 8.5 g/dL, and platelet count of 140 B/L. A comprehensive metabolic panel was grossly normal aside from a mildly elevated BUN and creatinine (21 U/L and 1.6 mg/dL, respectively). An orbital CT scan was quickly obtained due to the concern for a possible retro-orbital infectious process. The MRI scan revealed findings consistent with orbital cellulitis of the left eye with invasive sinusitis. The patient was emergently taken to the operating room for exploration and debridement of his maxillary, sphenoid, and ethmoid sinuses. Subsequent biopsies and cultures revealed a species of rhizopus fungi as the probable etiology of the patient’s symptoms. He was diagnosed with invasive mucormycosis involving the left orbit and sinuses.

The patient underwent multiple surgical procedures on his sinuses and left orbit. Intraoperatively, he received irrigation to the affected region with amphotericin B. He also received systemic therapy with amphotericin until he was noted to have worsening renal function. He was subsequently started on oral posaconazole with plans for a prolonged course of treatment. Following improvement in his symptoms he was discharged home with appropriate follow up with ophthalmology and infectious disease.

Discussion
Mucormycosis refers to an infectious condition caused by a variety of spore-forming organisms belonging to the zygomycetes class of fungi. These organisms are ubiquitous in nature, commonly being found in organic substrates such as soil, plant matter, and animal feces. Humans are routinely exposed but due to the intact functioning immune systems of the host, clinical disease is rare. However, in certain susceptible individuals a much more severe form of disease presentation can occur.

An important point in the discussion of mucormycosis is the terminology used to describe zygomycete infections. The class of zygomycetes is broken down into two subclasses: mucorales and entomophthorales. Mucormycosis refers to infections caused by the mucorales subclass of organisms. Within the mucorales subclass are multiple genera including mucor, rhizopus, rhizomucor, and absidia.

Mucormycosis was originally described in 1885 and up until the 1950s was considered an exceedingly rare diagnosis. However, with the sharp increase in certain susceptible populations (e.g.,
diabetics) over the past 50 years the diagnosis has become increasingly more common.\(^4\)

Mucormycosis has been described in a variety of different presentations with multiple organ systems being affected. Cerebral, pulmonary, renal, gastrointestinal, cutaneous, disseminated, and ophthalmologic forms have all been described. Disease can often spread locally to involve surrounding tissues such as the sinuses in our patient. Infection typically begins with inhalation of zygomycete spores into the nasopharynx during an environmental exposure. In the immunocompetent host, these spores are typically caught by the cilia of the respiratory tract, expectorated, and are of no further significance. However, if intact immune mechanisms are lacking in a host, local infection may begin with the germination of the spores into fungal elements called hyphae. Localized sites of infection can spread aggressively and become angioinvasive resulting in tissue infarction.\(^3\) Infection may also spread to distant sites via hematogenous routes. Other potential sites for initial infection need to be considered, such as those who abuse IV drugs and those with indwelling IV catheters. Most commonly patients possess some underlying risk factor for infection; however, case reports with no identifiable risk factor do exist.\(^4\)

Susceptible hosts usually possess a defect in the function of their mononuclear or polymorphonuclear phagocytes.\(^2\) Other immunosuppressive conditions can also confer risk. The most prevalent groups of patients who suffer these infections include those with diabetes, hematologic malignancies, neutropenia, acidotic states, solid organ or bone marrow transplants, as well as those who abuse IV drugs and those who are currently on deferoxamine iron chelation therapy.\(^2,5,6\)

Iron chelation therapy presents an interesting susceptibility to mucormycosis organisms. All microorganisms require iron to survive, and zygomycete organisms are especially sensitive to this requirement. In the past it has been observed that patients who carried a diagnosis of iron overload and were treated with deferoxamine chelation therapy seemed to suffer higher rates of mucormycosis than other populations.\(^1\) In the healthy patient, free available iron is scarce and difficult for organisms to obtain for growth as it is bound tightly with normal host proteins. However, in the patient with excess free iron (e.g., hemochromatosis), zygomycete organisms can exploit elevated levels of available free iron, and this can result in increased incidence of clinical disease. Even more susceptible is the patient being treated with deferoxamine. While this seems paradoxical, it is thought that zygomycete organisms can specifically use deferoxamine as a siderophore to sequester iron for growth thus promoting worsening disease.\(^7\) This phenomenon is not seen with other iron chelators. A similar susceptibility is found in patients with acidosis. This is believed to be secondary to the inability of proteins to effectively bind iron in acidic environments.\(^8\) The end result of this is additional free iron available to the invading zygomycete organisms.

Perhaps one of the most common examples of a susceptible host is seen in diabetics. The mechanisms of susceptibility are two-fold in these patients. Hyperglycemia is a known risk factor for neutrophil dysfunction and thus presents a risk for mucormycosis.\(^9\) In addition to this, the prominent acidotic states seen in patients suffering from diabetic ketoacidosis provide an optimal environment for mucormycosis infection.

Patient presentation is often dictated by the site of infection. Rhinocerebral mucormycosis is the most common form, comprising roughly 33% to 50% of all cases.\(^10\) Poorly controlled diabetics represent the major risk factor in this group.\(^1,2\) Patients often present with symptoms of sinusitis (e.g., headache, fever) combined with facial numbness secondary to involvement of the fifth cranial nerve. This can rapidly progress to involve surrounding tissues resulting in ocular involvement (e.g., blurred vision, proptosis, ophthalmoplegia, peri-orbital cellulitis), and in severe cases can advance into the central nervous system and surrounding vasculature often resulting in cerebral infarction secondary to carotid thrombosis or cavernous sinus thrombosis. A prompt diagnosis requires a high level of suspicion and an understanding of underlying risk factors for disease. Computed tomography (CT) and magnetic resonance imaging (MRI) may show non-specific evidence for soft tissue infection. Occasionally an eschar may be found on close examination of skin, nasal airways, or oral mucosa. Immediate consultation with an otolaryngologist is essential. While antifungal treatment is needed, survival and limitation of morbidity is usually dictated by prompt surgical debridement.

Pulmonary mucormycosis typically begins with inhalation of spores into the lungs; however, less common hematogenous and lymphatic spread from distant sites to the lungs has also been described. These patients most often are neutropenic, especially in the setting of chemotherapy and bone marrow transplant.\(^3\) Early complaints are often similar to pneumonia (e.g., fever, cough, dyspnea, and chest pain). More advanced disease can present with hemoptysis, often massive in quantity due to the angioinvasive nature of these infections.\(^3\) Diagnosis can be difficult due to non-specific symptoms and unreliable cultures. Because of these factors, tissue biopsy is usually required to confirm the diagnosis. Unfortunately mortality rates can range from 60% to 95% in pulmonary mucormycosis, with increasing mortality as the disease process becomes more invasive.\(^2\)

Cutaneous mucormycosis usually presents with local infection that has resulted from the breakdown of the normal barrier defenses in immunocompromised hosts as seen with traumatic injury, needle injections, and severe burns.\(^1\) Prognosis is good, and surgical therapy can be curative if pursued early; however, the potential for more severe disease is possible in cases left untreated.
Disseminated mucormycosis is perhaps the most severe form of zygomycete infection. Severe neutropenia, hematologic malignancies, iron overload, with or without deferoxamine therapy, and other forms of immunosuppression carry the greatest risk for this form of disease.\(^1\) Disseminated disease can spawn from any primary site of infection in the body; however, pulmonary disease is the most common source.\(^3\) The prognosis for these patients is dismal due to near absence of treatment options. Surgical therapy is not an option as the spread of disease is well beyond a focal source.

Other forms of mucormycosis are rare. Gastrointestinal manifestations involving the stomach, colon and ileum have been described.\(^6\) Similar risk factors are thought to play a role in these cases. Isolated CNS disease is rare in the absence of another primary site of infection. It is commonly seen with IV drug abusers and may present with focal neurologic deficits.\(^3\) Other isolated cases of different organ involvement have been described but the overwhelming majority of cases involve rhinocerebral, pulmonary, cutaneous, and disseminated forms.

The diagnosis of mucormycosis can be difficult due to the typically vague symptoms on presentation. Prompt diagnosis is of the utmost importance in terms of patient survival. An awareness of at-risk patient populations is needed in order to prevent a delay in confirming the patient’s diagnosis. Cultures are unlikely to yield timely results and may be contaminated due to the ubiquitous nature of the zygomycete organisms. Ideally, a tissue biopsy is obtained from an affected region of the patient’s body. Careful preparation of the specimen in the lab is important as typical grinding of specimens can destroy hyphal elements and delay diagnosis. Fine mincing of specimens is the suggested method for preparation and informing the lab of your suspicions will help in this matter. Laboratory diagnosis is based solely on microscopic appearance of hyphal elements. While thin, frequently-septated hyphal elements with regular branching suggest an alternative type of fungal species such as aspergillus, the identification of broad (5 to 15 micrometers), non-septated hyphal elements with irregular branching support a diagnosis of a zygomycete infection. Radiologic manifestations are unlikely to be diagnostic but can provide supporting evidence for a diagnosis. In the majority of medical centers there are no other methods of diagnosis in use such as PCR or serologic testing.

The treatment for mucormycosis is mostly surgical. Aggressive and complete resection of all infected tissue is vital to improving a patient’s chance of survival. Surgical consultation should be obtained as soon as possible and patients may often require multiple procedures to obtain adequate margins of resection. Serial imaging of affected tissues is done to monitor disease progression and may help guide further surgical procedures. With the exception of the last few years, the mainstay of medical therapy consisted solely of amphotericin B for the treatment of mucormycosis. More recently some experience with the use of posaconazole has expanded the options available to clinicians in the treatment of mucormycosis.\(^1,11,12\) While amphotericin B is known to carry multiple adverse effects including renal failure as seen in our patient, posaconazole is an alternative in patients who cannot tolerate amphotericin B.\(^13\) Posaconazole is available with oral dosing allowing for prolonged outpatient treatment which may be necessary in certain infections. Other antifungal medications possess little or no activity against zygomycete species and should not be used in any therapeutic regimen. The optimization or elimination of any predisposing risk factors (e.g., hyperglycemia, acidosis, neutropenia, etc.) should also be addressed as soon as possible to improve patient outcomes.

There is some interest in using iron chelation therapy as an adjunctive treatment to surgery and antifungal medications in the treatment of mucormycosis. Deferiprone (Ferriprox) is a potent iron chelator that has been used in thousands of patients outside the United States to successfully treat iron overload.\(^14,15\) Deferiprone, unlike deferoxamine, cannot be exploited by fungal species as a siderophore.\(^16\) This would potentially reduce free iron levels in patient serum, making it more difficult for fungal species to grow and reproduce. Ibrahim et al, in a rhizopus-infected DKA mouse model, were able to show significant improvements in survival of mice treated with deferiprone vs. placebo.\(^16\) The applicability in a human host is not proven at this time, and the use of deferiprone in the treatment of mucormycosis is available as compassionate use only.

The overall prognosis of patients diagnosed with mucormycosis is poor. Although outcomes have improved with the use of amphotericin B, mortality rates can approach greater than 80% in patients with pulmonary disease.\(^3\) Disseminated mucormycosis can result in mortality rates approaching 90% to 100%.\(^5\) Cutaneous disease, when addressed promptly with local surgical resection, carries the best prognosis with a greater than 90% survival rate.\(^2\) In most cases overall survival will be largely dictated by the underlying risk factors as well as the timeliness of surgical intervention.

In summary, mucormycosis represents a highly lethal type of infection typically affecting specific patient populations. Immunocompromised patients, diabetics and especially patients with DKA, oncology patients, patients with iron overload and those receiving treatment with deferoxamine should be viewed as having elevated risk for mucormycosis. Prompt consultation with a surgical team is of utmost importance and should not be delayed for a confirmed diagnosis. Systemic therapy with antifungal medication such as amphotericin B or posaconazole should be instituted quickly but should be viewed only as adjunctive to successful surgical resection. Overall prognosis is poor in most forms of disease with the exception of mild localized cutaneous disease.
References

A Tale of Two Women: Is There a Benefit to Bilevel Ventilation in Pregnancy?
Laura Immordino, MD, and Adam Kaufman, MD

Case Presentation 1
The patient is a 24 year-old pregnant female at 31 and 6/7 weeks estimated gestational age, who presented to the emergency department with complaint of intermittent right-sided abdominal pain, nausea, vomiting and fevers over the past twenty-four hours. The patient’s vital signs at presentation were significant for a heart rate of 130 beats/minute and a blood pressure of 90/32 mm Hg. Her physical examination was otherwise unremarkable, and she was initially admitted to the maternal-fetal medicine service and started on intravenous fluids. Over the next 12 hours, the patient remained tachycardic with blood pressures in the 80s/40s. She began to develop respiratory distress, and an ICU evaluation was requested.

At the time of evaluation, the patient’s physical exam revealed a well-developed, gravid woman in moderate distress. Her temperature was 100.7º Fahrenheit, pulse was 136 beats/minute, blood pressure was 94/41 mm Hg, respiratory rate was 38 breaths/minute, and pulse oximetry was 99% on a 100% non-rebreather mask. She was anicteric with moist mucous membranes and normal skin turgor. On cardiac examination, her heart rate was tachycardic and regular, without any murmurs. Her lungs were clear to auscultation and abdomen was soft and gravid without any tenderness to palpation. She had no peripheral edema. On vaginal exam, her cervix was long and one centimeter dilated.

Laboratory results were significant for a white blood cell (WBC) count of 19.8 B/L and CO2 of 17 mmol/L. Arterial blood gas was 7.46/25/125/18/99% on a 100% non-rebreather mask. Broad spectrum antibiotics were started, and a stat CT of the chest, abdomen and pelvis was performed, which showed dense consolidation of the left lower lobe, consistent with pneumonia.

The patient was maintained on a non-rebreather with stable oxygen saturations for several hours, but eventually decompensated, requiring emergent intubation. She was initially placed on assist-control ventilation; however, her oxygen saturations remained in the 60s to 70s. She was noted to have decreased left-sided breath sounds, despite pulling back the endotracheal tube. A stat chest radiograph was performed, which showed near complete collapse of the left lung.

The patient was subsequently switched to bilevel ventilation with eventual improvement in her oxygenation (see Figures 1 and 2). She initially required high level settings, with an inspiratory/ expiratory pressure of 35/10 mm Hg. The patient’s status improved over the next few days with antibiotic treatment, and cultures all remained negative, but serologies were positive for Mycoplasma IgM. Pressure support was discontinued on hospital day four, and ventilatory support was titrated down slowly over the next few days. On hospital day seven, the patient was successfully extubated. Antibiotics were narrowed to oral azithromycin to complete a fourteen day course of antibiotics for mycoplasma pneumonia.

Case Presentation 2
The patient is a 19 year-old pregnant woman at 29 and 6/7 weeks estimated gestational age, transferred from an outside hospital to the maternal-fetal medicine service with complaints of nausea, vomiting and fever for one week. Over the past twenty-four hours, the patient complained of increasing abdominal pain and developed fevers to 103º Fahrenheit.
The patient had no significant past medical or gynecologic history. She denied any previous surgeries or allergies to medications. On transfer from the outside hospital, she was receiving intravenous ampicillin, ceftriaxone, betamethasone and fluids.

Several hours after admission, the patient began to develop respiratory distress, and an ICU evaluation was requested. At that time, physical examination revealed a well-developed, gravid woman in moderate to severe distress. Her temperature was 102.3°Fahrenheit, pulse was 127 beats/minute, blood pressure was 115/58 mm Hg, respiratory rate was 34 breaths/minute, and pulse ox was 98% on a 100% non-rebreather. She was noted to have moist mucous membranes, scleral icterus, and tachycardia without murmurs. The remainder of the exam was significant for bilateral rales and mild abdominal tenderness to palpation diffusely, without rebound or guarding. She was noted to have mild lower extremity pitting edema. Neurologic exam was within normal limits.

Laboratory studies revealed a WBC count of 9.7 B/L, hemoglobin of 8.1 g/dL, and platelet count of 162 B/L. Her basic metabolic panel was within normal limits; however, liver panel showed elevated total and direct bilirubin levels of 4.8 and 2.2 mg/dL. AST of 698 U/L, ALT of 293 U/L, and alkaline phosphatase of 193 U/L. LDH was 1169, fibrinogen was 326, and D-dimer was elevated at 10.21. A diagnostic amniocentesis was performed, which showed no evidence of chorioamnionitis. Chest radiograph at that time showed bilateral infiltrates.

Hepatitis serologies, autoimmune, and vasculitis studies were negative. Blood, urine, and bronchoalveolar lavage cultures for viral, bacterial, and fungal infections were negative. Hematologic work-up revealed no evidence of microangiopathic anemia, and HUS/TTP was ruled out. Echocardiogram showed no evidence of tamponade, lower extremity ultrasounds were negative for deep venous thromboembolism, and abdominal ultrasound showed no obvious liver pathology. Results from the outside hospital were only significant for a positive Mycoplasma IgM.

The patient remained febrile in the range of 102° to 103° Fahrenheit for nearly two weeks, despite empiric treatment with broad-spectrum antibiotics. On hospital day five, the patient’s respiratory status deteriorated requiring intubation. She was placed on assist control ventilation with a respiratory rate of 20, tidal volume of 400cc, PEEP of 5, and FiO2 of 50%. On hospital day seven, the patient’s oxygenation dropped, requiring 100% FiO2. At this time, her ventilator settings were changed to ARDS protocol, and the FiO2 was titrated down over the next few days. On hospital day 16, the patient was noted to have high peak inspiratory and plateau pressures, with PaO2 ranging from 65 to 90. On hospital day 18, in order to facilitate weaning, the patient was placed on bilevel ventilation with inspiratory/expiratory pressures of 30/5. Prior to the ventilatory switch, her PaO2 was 90% on 50% FiO2; following the mode change, her PaO2 was 167% on 50% FiO2. The inspiratory pressures were titrated down over the next few days, and on hospital day 23 she was placed on pressure support of 18. She was weaned to a 40% tracheal collar on hospital day 27, and transferred out of the ICU on hospital day 24.

**Discussion**

Bilevel ventilation is a form of partial ventilatory support, which allows for spontaneous breathing at any point in the ventilator cycle. It is a time-triggered, pressure-limited, and time-cycled mode of ventilation. Inspiratory and expiratory pressures are set as PEEP high and PEEP low, and the physician is able to set length of time for the PEEP low. The goal of PEEP high is to help open the consolidated portions of the lungs that are often present in patients with acute lung injury or ARDS. PEEP low is a pressure release phase that allows for lung recoil and CO2 removal. A built-in valve allows for spontaneous breathing throughout the respiratory cycle.1,2 Spontaneous breathing has been shown to preferentially recruit dependent lung regions while simultaneously allowing for less neuromuscular blockade and sedation.1,4

In traditional mechanical ventilation, the majority of ventilation occurs centrally as opposed to at the distal alveoli, where the majority of perfusion occurs. The goal of bilevel ventilation is to increase alveolar recruitment which leads to decreased shunting, better arterial oxygenation, and improved ventilation-perfusion matching.7,8 By allowing for spontaneous breathing throughout the respiratory cycle, bilevel ventilation results in increased patient comfort and thus a decreased need for sedation and neuromuscular blockade.6 Since excessive sedation has been associated with a longer duration of intubation, decreased cough reflex, and increased risk of ventilator associated pneumonia, many studies have suggested that the use of bilevel ventilation can lead to a shorter ICU and hospital length of stay.5,8

Contraindications to bilevel ventilation include patients with COPD (as they are at risk of barotrauma) and patients with neurologic disorders with increased intracranial pressure (as permissive hypercapnea is contraindicated in these patients).1,4,8

**References**


**A Woman With Massive Splenomegaly**

*Erin Meschter, MSIII, Michelle Choi, MD, and Lisa Teng, MD*

**Case Presentation**

An 82 year-old Caucasian woman was admitted to the hospital with marked splenomegaly and pancytopenia. Her primary care physician noted splenomegaly on physical exam during a recent visit, and a CT scan of the abdomen was performed as an outpatient which revealed a massively enlarged spleen. The patient admitted to losing up to 40 pounds over the past six months due to decreased appetite and early satiety. She also reported dyspepsia and a feeling of fullness in her belly for several months. The patient denied nausea, vomiting, constipation, or diarrhea. Other symptoms included increased fatigue, chronically swollen legs, and frequent night sweats two to three nights per week with occasional fevers. The patient denied shortness of breath, cough, or chest pain. She complained of urinary urgency and frequency.

The patient had a past medical history of hypertension and osteoarthritis in her knees and ankles. Her past surgical history included cataract surgery and cholecystectomy. Family history was significant for her mother’s “heart problems” and her father dying from pneumonia. The patient had never smoked, although she frequently experienced second hand smoke. She did not drink, nor did she have a history of alcohol abuse. She never used any illegal drugs or recreational substances. Medications included Clonidine 0.1 mg BID and hydrochlorothiazide 12.5 mg every day. She had no known drug allergies.

On physical exam her temperature was 97.8° Fahrenheit, pulse was 98 beats/minute, and respiration rate was 19 breaths/minute. Her blood pressure was 129/71 mm Hg, and her oxygen saturation was 98% while breathing ambient air. The patient was in no apparent distress and was alert and oriented to time, place, and self. She was slender with a protuberant abdomen. The spleen was palpable beyond the umbilicus into the right upper quadrant. She had no lymphadenopathy. She was pale, but not jaundiced, and had no apparent ascites. She had a 2/6 systolic ejection murmur with no heave and a normal PMI. Her lungs were clear to auscultation bilaterally. She had numbness in her index and ring finger on both hands and some left-sided facial numbness in the distribution of the V2 branch of cranial nerve five. Neurologic exam revealed no other abnormalities. She had no joint swelling or erythema, but her legs had pitting edema bilaterally.

On admission, chest radiograph and CT of the abdomen with contrast showed massive splenomegaly (24.5 X 15.1 X 11.7 cm, see Figure 1). Her CBC revealed pancytopenia with a white blood cell count of 2.4 B/L, red blood cells 3.36 B/L, platelets 94 B/L, hemoglobin 10.6 g/dL, and hematocrit 32.8%. Reticulocyte count was elevated at 2.1%. Of note, she had an elevated lymphocyte count of 45.5; neutrophils were low at 36.4. Electrolytes were within normal limits. Albumin was low at 2.9 g/dL and LDH was normal at 199 U/L. Her blood smear showed pancytopenia consistent with her complete blood count along with poikilocytosis and suspected villous lymphocytes. Vitamin B12 was very low at 52 pmol/L. A Monospot test was non-reactive.

A bone marrow biopsy was performed a few days after admission along with flow cytometry. The bone marrow biopsy indicated patches of hypercellularity with lymphoid aggregates consisting of monotonous, small round cells without cytoplasm suggestive of small lymphocytes. Paratrabecular aggregates also were appreciated. The bone marrow had maintained good hematopoietic activity. Of note, reticulin staining of the bone marrow was increased in the aggregates indicating that this bone marrow was more difficult to aspirate and thus aggregate cells may have been less represented on smear. Markers were used to stain the bone marrow. A marker for CD3 was used to stain T cells, which were sprinkled throughout the bone marrow with a few in the lymphoid aggregates. A marker for CD20 was used to stain B cells, which were scattered throughout the marrow. Lymphoid aggregates were predominantly CD20 positive, suggestive of a B cell lymphoproliferative disorder.

Flow cytometry was used to distinguish what type of lymphoproliferative disorder was present in this woman’s bone marrow. Total lymphocytes were 35%, which is slightly elevated. Of the lymphocytes, 31% were B cells (15% to 20% is normal). The B cells present were CD10 negative, which eliminated follicular cell lymphoma from the differential. The B cells were CD5 negative, making Mantle cell lymphoma and chronic lymphocytic leukemia (CLL) less likely. There were some B cells that were CD11c positive, a marker for Hairy cell leukemia; but a more specific marker for Hairy cell is CD103, which was negative in this patient’s bone marrow biopsy. Most revealing was the kappa and lambda Ig marker staining, which is used to evaluate for clonality. The flow cytometry showed kappa restricted B cell clonality (see Figure 2). Through a process of elimination via this analysis, a diagnosis of splenic marginal zone lymphoma (SMZL) was suspected. There are no distinguishing markers for SMZL, and this type of lymphoma shares many markers with other lymphoproliferative diseases. It is interesting to note that there is CD15 positivity in the B cells present in this patient, and perhaps this marker should be followed in future diagnoses of SMZL to discover a new correlation.

**Discussion**

Splenic marginal zone lymphoma (SMZL) is an indolent B-cell malignancy involving the spleen, bone marrow, and blood. It is a rare lymphoma type, first described in 1992, and has been estimated as less than 2% of all patients with lymphoma. Almost all patients...
present with moderate to massive splenomegaly, sometimes with abdominal discomfort. Hepatomegaly can sometimes be observed, but lymphadenopathy is uncommon. Anemia and thrombocytopenia are common at presentation secondary to hypersplenism more than bone marrow infiltration. Autoimmune phenomena, such as primary biliary cirrhosis, rheumatoid arthritis, immune thrombocytopenia, are present in 10% to 20% of patients. Splenic marginal zone lymphoma is considered a low-grade lymphoma with an indolent clinical course, and median survival is close to ten years, with five-year survival estimated to be greater than 65%. Approximately 10% of patients undergo transformation to a high-grade lymphoma.

The diagnosis is based on lymphocyte morphology, immunophenotype, bone marrow histology, cytogenetic abnormalities, and when available, spleen histology. Approximately 75% of patients with splenic marginal zone lymphoma will have a peripheral blood lymphocytosis. One of the most characteristic findings is the presence of villous lymphocytes on peripheral blood smear, which are intermediate-sized lymphocytes with condensed chromatin and short cytoplasmic projections. However, the amount of circulating cells may be so small, that it cannot be detected. Infiltration of the bone marrow is evident in virtually all patients with SMZL, but is invariably involved. It may be demonstrable only by flow cytometry and not by morphology alone. The immunophenotype profile for SMZL is typically positive for CD20, CD45RA, CD45RB, CD79A, PAX5/BSAP, IgM, and bcl2, and negative for CD43, CD23, CD10, bcl6, and cyclin D1.

The pattern of bone marrow infiltration can vary and may be nodular, intrasinusoidal, interstitial, and paratrabecular. However, intrasinusoidal infiltration is considered to be characteristic of SMZL. In SMZL, the spleen is enlarged and splenic sections demonstrate a nodular replacement of white pulp, usually with a central core of lymphocytes with slightly irregular nuclei, and an outer zone of larger cells with clear cytoplasm in the marginal zone. Both cell populations are part of the neoplastic clone. The splenic red pulp is also involved in most cases, usually occupying germinal centers and is evident by immunostaining. Although a primary diagnosis of SMZL is rarely, if ever, made on the basis of lymph node biopsy, splenic hilar nodes are typically involved. Complex chromosomal aberrations are common in SMZL; 80% of cases have an abnormal karyotype, but there is no single abnormality present in all cases. The most frequent cytogenetic aberrations are gains of 3q and 12q and 7q deletion.

There is no definitive standard treatment for splenic marginal zone lymphoma to date. The level of evidence supporting recommendations for initiating treatment is weak due to the absence of prospective clinical trials. Currently treatment is based on clinical evidence obtained from clinical centers with experience in treating SMZL. Due to the indolent course of SMZL, about two thirds of patients are asymptomatic at diagnosis and as many as one third will never require therapy. In general, the development of lymphadenopathy, high lymphocyte count, or infiltration of non-hematopoietic sites have been found to be associated with progression and shorter overall survival. Progression may also be associated with a transformation to a high grade lymphoma.

However, therapeutic intervention should be considered in patients with active disease. Considering the indolent course of SMZL, the patient’s age and comorbidities, treatment should be aimed at achieving control of the disease and symptoms rather than eradication of the disease. There are several therapeutic options effective in these patients including splenectomy, chemotherapy, and irradiation. Symptomatic splenomegaly or severe cytopenia are the main indications to perform splenectomy. However, splenectomy alone cannot reduce the extrasplenic lymphomatous infiltrations, and one group has reported an increase of tumor burden in the bone marrow after splenectomy.

Splenic irradiation has been used in a limited number of patients and has been reported to produce a reduction in circulating villous lymphocytes, regression of splenomegaly, and improvement of cytopenias. Chemotherapy is generally used as a first line treatment in people with more advanced disease. Alkylating agents appear to be of marginal benefit. Purine analogs, such as fludarabine in combination with rituximab, or rituximab alone, have demonstrated a greater efficacy than alkylating agents in terms of response and progression-free survival.

Our patient’s clinical presentation and findings were consistent with splenic marginal zone lymphoma. She received splenic irradiation and underwent splenectomy for symptomatic splenomegaly. She is currently undergoing chemotherapy with Rituxan.
Figure 2. All three flow cytometry graphs show kappa-restricted B cell clonality, suggestive of a B cell lymphoproliferative disease. Graph A shows only kappa positive marker; the same cells are negative for lambda marker. CD19 is a marker for B cells, and is utilized in Graph B and C. Graph B displays CD19 positive cells are also kappa positive, but they are lambda negative (in Graph C).

References
A CASE OF DIABETIC MUSCLE INFARCTION DESPITE GOOD DIABETIC CONTROL
Tessey Jose, MD, and Intekhab Ahmed, MD

Case Presentation
A 52 year-old female with type 2 diabetes of 10-year duration was admitted with worsening of shooting pain and swelling of her lower extremities over the previous nine days. The pain was rated 10/10 in severity, was worse in the right side as compared to the left, radiated from her lower legs to thighs, and limited her mobility for the previous five days. She reported no history of trauma, fever, chills, skin changes, or medication noncompliance. She was managing her diabetes with two injections of premixed insulin. Her other medical problems include a history of congestive heart failure with an ejection fraction of 45%, coronary artery disease, stage 4 chronic kidney disease, and hypertension. A review of systems was remarkable for exertional dyspnea and mild ascites.

On admission, the patient was afebrile, had blood pressure 147/101 mm Hg, a regular pulse of 88 beats/minute, respiratory rate of 18 breaths/minute, and pulse oximetry of 100% on two liters of oxygen via nasal cannula. Cardiovascular exam was benign except for scattered crackles at the bases on deep inspiration. A musculoskeletal examination revealed tender, edematous lower extremities up to the top third of her thighs without any skin excoriation or ulceration. All pulses were palpable with normal pressure and volume in both extremities. Neurological exam was only significant for inability to walk secondary to pain and swelling.

The laboratory work-up revealed a hemoglobin A1C level of 6.5%, fasting blood glucose of 95 mg/dL, serum creatinine of 3.4 mg/dL, white blood count (WBC) of 17.1 B/L, and an erythrocyte sedimentation rate (ESR) of 95 mL/hr.

A diuretic was initiated to lessen lower extremity edema as it was initially thought to be due to congestive heart failure. Lower-extremity ultrasound was negative for deep vein thrombosis, and a blood culture was negative. Magnetic resonance imaging (MRI) of lower extremities revealed diffuse swelling and edema involving the tensor fascia lata with areas of muscle replaced by fluids in both legs especially in the thigh area (Figures 1 and 2).

A diagnosis of diabetic myonecrosis was made on the basis of MRI findings, raised ESR, and elevated WBC in the absence of negative blood cultures and fever. The patient was managed with supportive care and analgesia as needed.

Discussion
Diabetic myonecrosis is a rare complication of diabetes, first described in 1965 and known to affect patients with poorly controlled diabetes of long-standing duration. Most common presentation of diabetic myonecrosis is acute lower extremity pain and swelling involving calf and thigh. These patients often have established nephropathy, retinopathy, and a long-standing history of poor glycemic control.

Figures 1 and 2. Coronal Image - T2 weighted with fat saturation. The image shows diffuse swelling involving the entire right tensor fascia lata with areas of muscle replacement by fluid, findings consistent with diabetic myonecrosis. There is also swelling of the left adductor magnus, which may represent diabetic myopathy versus early diabetic myonecrosis.
The pathophysiology of diabetic myonecrosis is not completely understood. The possible contributing role of atheromatous emboli, thrombo-occlusive disorder, and arteriosclerosis has been implicated in some cases.\(^2\)

<table>
<thead>
<tr>
<th>Table 1. Differential Diagnosis of Acute Lower Extremity Swelling.</th>
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<tr>
<td>Deep Vein Thrombosis</td>
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<td>Thrombophlebitis</td>
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<td>Trauma</td>
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<td>Diabetic Myotrophy</td>
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<tr>
<td>Myositis Ossificans</td>
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<td>Muscle Strain or rupture</td>
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Laboratory tests typically reveal leukocytosis, elevated C reactive protein, and creatinine kinase in 35%, 75%, and 45% of cases, respectively.\(^3\) Histological features of diabetic myonecrosis consist of large areas of muscle necrosis and edema.\(^4\) Diagnosis is primarily made through clinical suspicion and on MRI. Recurrence is common and has been reported in up to 50% of cases. Diabetic myonecrosis is a self-limited condition, which resolves on its own within weeks to months. Treatment is supportive care with analgesia, rest, and optimal glucose control. Physical therapy is not recommended, as it may acutely aggravate necrotic muscle.

**Conclusion**

After reviewing the literature, this case is one of the first reports of diabetic myonecrosis in a well-controlled diabetic patient. This case demonstrates that the diagnosis of myonecrosis should be considered even in well-controlled diabetics in the setting of acutely painful, swollen lower extremities in patients with long-standing diabetes.

**References**

Case Presentation
An 81 year-old male who resides in Florida presents to the emergency department (ED) with complaints of weakness, 20 pound weight loss, and decreased appetite over the last six months. He is currently in the Philadelphia area to visit his son, and after his concerned son heard of these complaints, he brought his father to the ED. The patient indicates that he has become progressively weak over the last six months. He has also been increasingly fatigued, finding it difficult to walk even two blocks. A year ago, the patient walked two to three miles a day without a problem. Past medical history is significant for coronary artery disease, although he reports a normal stress test three months ago, stroke in 2004 with residual dysarthria, and melanoma on chest wall diagnosed in 2005 status-post resection. He lives with his wife and is a retired interior architect. He has not drunk alcohol in two years, has not smoked cigarettes in 20 years, and has never used illicit drugs. There is no history of cancer in his family, but significant history of stroke in his mother and sister. He saw his primary care physician for these symptoms in Florida, and a diagnosis had not been reached, but the patient indicates that he had a PET scan and a needle aspiration done on his right lung in the last month. He does not know the results of these tests.

On presentation, the patient was afebrile with a temperature of 97.0° Fahrenheit, blood pressure of 164/77 mm Hg, heart rate of 57 beats/minute, and respiratory rate of 20 breaths/minute with pulse oximetry of 94% on room air. Physical exam was unremarkable, including the neurological exam. His cranial nerves, motor, sensory and cerebellar functions were all intact. Reflexes were 2+ bilaterally in the upper and lower extremities, and patient had a normal gait.

This gentleman was admitted to the general floors, and given the patient’s symptoms of weight loss, weakness, and decreased appetite, an occult malignancy seemed to be the most likely diagnosis. Chest radiograph on admission showed an ill-defined density in the right infrahilar region. PPD, HIV and ANA tests were negative, but ESR and CRP were elevated suggesting an inflammatory etiology. CT scan of the head, chest, abdomen, and pelvis was done on hospital day two. CT head without contrast showed no mass effect, bleed or intracranial lesions. CT chest, abdomen, and pelvis showed bilateral pleural effusions, ground glass opacities in both upper lobes, nonspecific scattered centrilobular nodules, consolidation/atelectasis in posterior segment of right lower lobe, three 0.5 cm nodules in the right lower lobe, and an infiltrative soft tissue mass surrounding both proximal collection systems in the retroperitoneal region.

On hospital day seven, PET scan results were obtained from Florida which showed right lung lower lobe and left lung lower lobe enhancement with greater attenuation found in the right basilar lung region. Right lung needle aspiration results from Florida obtained on hospital day nine were consistent with fibrotic tissue and no evidence of malignancy. The cardiothoracic surgeons were consulted to evaluate the patient for a VATS procedure in an attempt to obtain a tissue biopsy of the enhancement in the right lower lobe. MRI abdomen indicated that the soft tissue mass shown on CT abdomen and pelvis was consistent with retroperitoneal fibrosis and not malignancy. Despite the results of the needle aspiration from Florida, a repeat biopsy was scheduled via VATS on the right lower lobe of the lung. A right-sided chest tube was kept in place after the VATS, but was only necessary for one day. Pathology slides read two days later revealed pulmonary hyalinizing granulomas.

Figure 1. (left) CT chest demonstrates pathology in the right lower lung region and specifically, a 5.2mm nodule.

Figure 2. (right) Bilateral ground glass opacities.
Discussion
Pulmonary hyalinizing granulomas were first described by Engleman et al in 1977. Just less than 100 cases have been reported since then. Symptoms include hemoptysis, pleuritic chest pain and cough. Retroperitoneal fibrosis has been known to be associated with this condition. The disease is rare and idiopathic, but an autoimmune response is one of the leading theories to explain its etiology. Autoantibodies and circulating immune complexes have been detected in a few patients. The pulmonary lesions in these patients have been known to enlarge or regress spontaneously, and a search for an inciting factor for these events has so far been fruitless. In Thorax, an article by Dent et al in 1983 discussed a patient with a diagnosis of pulmonary hyalinizing granulomas and retroperitoneal fibrosis who worked in the oil industry for many years and had copious exposure to toxic fumes. There was some thought that oil could be an instigator of these spontaneous growths of the granulomas, but the histology did not support this theory as there were not many mineral oil droplets present on the slides. A typical histologic slide consistent with pulmonary hyalinizing granulomas shows densely matted, stout, hypocellular collagen fibers with fine granular stippling with sporadic calcium deposits. The presence of amyloid fibers can co-occur with these granulomas also.

The biopsy results for our 81 year-old male were consistent with pulmonary hyalinizing granulomas. Initially, there were plans to biopsy the retroperitoneal fibrosis after the patient’s VATS, but given previous case reports describing a strong correlation between retroperitoneal fibrosis and our primary diagnosis, the biopsy never occurred. This patient was started on high dose prednisone at 80 mg by mouth once a day. He was to be tapered off of the prednisone slowly. After a few days of treatment, the patient’s weakness and appetite improved. The patient received physical therapy for a couple more days and was discharged from the hospital. The patient is to follow up closely with his primary care physician in Florida.

References
Hemoptysis as a Presenting Symptom for Metastatic Pancreatic Cancer

Toshimasa Okabe, MD, Leigh Van Vranken, MSIII, and Darren N. Seril, MD

Introduction
Approximately 32,000 pancreatic neoplasms are diagnosed in the United States annually. Currently, carcinoma of the pancreas is the fourth most common cause of cancer death in both men and women in this country, after cancers of the lung, breast/prostate, and colon. The most common presenting symptoms of pancreatic cancers are epigastric pain, obstructive jaundice, and weight loss. However, since pancreatic cancer is frequently metastatic when diagnosed, it may uncommonly present with findings characteristic of the site of spread.

Case Presentation
A 42 year-old Caucasian female with no significant past medical history presented with a four-month history of daily hemoptysis associated with a productive cough and a two-week history of jaundice and gray stools. The initial evaluation for hemoptysis, performed at an outside hospital approximately three months prior to presentation included a normal chest radiograph and negative PPD. Two weeks prior to admission, the patient presented to an outside hospital complaining of epigastric pain for one week, as well as new onset jaundice and persistent hemoptysis. Per the patient, an abdominal ultrasound performed at that time revealed a pancreatic mass. She presented shortly thereafter to our hospital with worsening hemoptysis, epigastric and right upper quadrant pain, and jaundice. She described the abdominal pain as constant and dull, with an intermittent stabbing component. The pain was aggravated when lying down and relieved by oxycodone-acetaminophen. She also reported generalized fatigue and a five-pound weight loss over three weeks.

She denied fever, chills, night sweats, chest pain, shortness-of-breath, nausea, vomiting, or diarrhea. She has no known drug allergies. Her only medication was oxycodone-acetaminophen which was started for abdominal pain during the previous hospital visit. She has no history of abdominal or other surgeries. She consumes three to four drinks of alcohol per week during the past two years and has smoked approximately one pack of cigarettes per day for the past 25 years. She used cocaine on occasion more than 10 years ago. She denied intravenous drug use. Her mother, a smoker, died from small cell lung cancer, and her father died from prostate cancer. She denied recent travel, as well as known exposure to individuals with tuberculosis, asbestos, or other inhaled chemicals.

Figure 1. PA and lateral chest radiographs shows showed no evidence of infiltrates, effusions, or masses.
Case Reports

Hospital Course

Initial examination revealed a jaundiced but well-appearing middle-aged woman in no acute distress. Vital signs revealed a temperature of 98.7° Fahrenheit, blood pressure 92/62 mm Hg, heart rate 70 beats/minute, respiratory rate of 18 breaths/minute, and oxygen saturation of 96% while the patient was breathing ambient air. The sclerae were icteric. The lungs were clear to auscultation bilaterally without wheezes, rales, or rhonchi. Abdominal exam revealed tenderness on palpation of the right upper quadrant and epigastrium without rebound tenderness or guarding. No Murphy’s sign was detected. The skin was jaundiced without rashes, spider angiomata, or palmar erythema.

The remainder of the physical examination was unremarkable.

The results of the laboratory tests were significant for total bilirubin 10.8 mg/dL, direct bilirubin 4.9 mg/dL, AST 148 IU/L, ALT 196 IU/L, and alkaline phosphatase 225 IU/L. CEA was 1.1 ng/mL (normal range: 0.0-5.0 ng/mL) and CA 19-9 was 12 ng/mL (normal range: 0.0-36.0 U/mL). Her complete blood count, basic metabolic panel including creatinine, protein, albumin, amylase, lipase, PT, and PTT were within normal limits.

A chest radiograph obtained on admission showed no evidence of infiltrates, effusions, or masses (Figure 1). A chest CT with contrast performed at an outside hospital two weeks prior to presentation revealed a cavitary lesion in the anterior segment of the left upper lobe. The lesion was confirmed by repeat CT scan (Figure 2) and measured 2.6 X 2.5 cm, with no marked changes in size or appearance from the prior study. Several small lung nodules were noted as well. In addition, enlarged mediastinal lymph nodes measuring 10 mm in diameter were noted in the hila bilaterally. Multi-detector abdominal CT with contrast (Figure 3) revealed a pancreatic head mass measuring 3.5 X 3.3 cm, with abdominal lymphadenopathy, and intra- and extra-hepatic biliary ductal dilatation.

Based on these findings, the initial differential diagnosis included a metastatic neoplasm of either pulmonary or pancreatic origin. Disseminated tuberculosis or other bacterial or fungal infection, as well as a vasculitic process, were also considered. Anti-neutrophil Cytoplasmic Antibody (ANCA) serologies were obtained and were negative. ESR was 22 mm/hr (normal range: 0-15 mm/hr) and CRP was 0.7 mg/l (normal range: <12 mg/L).

For diagnostic and therapeutic purposes, endoscopic retrograde cholangio-pancreatography (ERCP) was performed. A common bile duct (CBD) stricture was noted, and brush cytology of the CBD was obtained. Subsequently, an expandable metal stent was placed in the CBD after sphincterotomy. In order to further evaluate the pancreatic mass, endoscopic ultrasound (EUS) was performed, and fine needle aspiration (FNA) biopsy of the mass was performed. Bronchoscopy was performed to further evaluate the cavitary lung lesion noted on CT scan. Bronchoalveolar lavage (BAL) and bronchial brushings were sent for cytology, Gram stain, and culture. Endobronchial ultrasonography-

Figure 2. CT thorax with contrast illustrates a cavitary lesion in the anterior segment of the left upper lobe (arrow).

Figure 3. Multi-detector CT abdomen and pelvis with contrast detects a hypodense mass in the head of the pancreas (arrow).
**Discussion**

Pancreatic cancer is notoriously aggressive. Indeed, surgically resectable cases on presentation represent the minority: approximately 10% to 15%. Pancreatic neoplasms metastasize by hematogenous and lymphatic routes. Locally, the celiac plexus, superior mesenteric artery, portal vein, and ligament of Treitz are common sites of spread. The liver appears to be the most frequent target of distant metastasis, as well as the peritoneum. The lung is also a common target. Lung metastases were present in greater than 50% of patients with metastatic pancreatic cancer in one study.2

It is rare for metastatic pancreatic cancer to present initially with pulmonary symptoms. Nevertheless, there are case reports of pancreatic cancer “masquerading” as bronchogenic carcinoma, with initial symptoms including cough and dyspnea, as well as those related to paraneoplastic syndromes, i.e., Horner’s syndrome.3 It has been shown that pancreatic metastases can be radiographically indistinguishable from primary bronchogenic carcinomas,4 highlighting the importance of obtaining biopsy for tissue diagnosis and to guide treatment.

The treatment of pancreatic cancer is broadly based on staging of the disease to determine resectability. With the exception of lymph node spread restricted to the surgical field, metastasis renders pancreatic cancer unresectable. The median survival after diagnosis is extremely poor in the case of unresectable pancreatic cancer: approximately three to five months.1 Surgical resection via partial pancreaticoduodenectomy (i.e., the Whipple procedure), typically with adjuvant chemotherapy, is the only treatment modality with any meaningful survival benefit. Median survival can be extended to 12 to 18 months with surgery and still further in conjunction with chemotherapy.5 The treatment of unresectable pancreatic cancer, including distantly metastatic disease, is essentially palliative and entails management of symptoms, including pain, jaundice, and malabsorption.1

The most common findings in the setting of pancreatic cancer include jaundice and abdominal pain. Other findings include Courvoisier’s sign (i.e., a palpable nontender gallbladder) and Trousseau’s syndrome (i.e., superficial and deep venous thrombosis), as well as more vague symptoms such as fatigue and weight loss.6 The presentation is often suggestive of the site of the pancreatic mass. Tumors of the head of the pancreas tend to present with jaundice. Pain is often a later finding, associated with tumors of the pancreatic body and tail. Back pain is an ominous sign, as it may indicate local spread to the lesions within the left upper lobe of the lung, left adrenal gland, and L1 vertebral body. The patient later initiated chemotherapy as an outpatient for palliation of widely metastatic pancreatic cancer. She was given a final diagnosis of primary pancreatic adenocarcinoma metastatic to the lung, adrenal gland, and spine.

![CT-guided biopsy of anterior lung mass.](image)

**Figure 4.** CT-guided biopsy of anterior lung mass.
celiac neuroplexus posterior to the pancreas. The present case is unusual in that pulmonary symptomatology preceded the more typical findings of abdominal pain and jaundice. Because pancreatic head cancers often impinge on the CBD and cause jaundice, these cancers can sometimes be detected at an earlier, less advanced stage than cancers of the body or tail, which are all frequently metastatic to distant sites before pain in the abdomen or the back emerges.

In addition to metastatic pancreatic or lung cancer, our differential diagnosis for the concurrent findings of a cavitary lung lesion and pancreatic mass included atypical infections, such as mycobacterial and fungal infections, other granulomatous diseases, and systemic vasculitides, such as Wegener’s granulomatosis. Tuberculosis was a consideration in the present case, although less likely in the context a negative PPD and lack of a suggestive exposure history. Sarcoidosis is well known to involve multiple organs, including the respiratory system, skin, eye, heart, and liver. There are case reports of rare involvement of the pancreas, causing symptoms similar to pancreatic cancer. Wegener’s granulomatosis has been reported to manifest like pancreatic carcinoma as well. Interestingly, the patient in the present case reported intermittent sinus symptoms, but negative ANCA serologies and a lack of renal involvement made this hypothesis less likely. Ultimately, tissue sampling of the lung and pancreas masses by CT guidance and EUS-FNA proved critical in establishing a definitive diagnosis in this case.

In summary, the current case represents an uncommon presentation of metastatic pancreatic adenocarcinoma, characterized by jaundice and abdominal pain preceded by a prolonged period of respiratory symptoms alone.

References

Photograph courtesy of Sandarsh Kancherla, MD
Case Presentation

A 62 year-old female with severe chronic obstructive pulmonary disease and chronic Aspergillus mycetoma developed the sudden onset of dyspnea on post-operative day two after a posterior cervical spine laminectomy for severe arthritis. This single image from her contrast-enhanced thoracic CT shows the 10 cm left upper lobe pulmonary fungal ball, a new extensive left lower lobe Klebsiella pneumonia, and an acute right lower lobe pulmonary embolus.

Figure 1. CT chest show large pulmonary fungus ball in the left upper lobe, left lower lobe pneumonia, and acute right lower lobe pulmonary embolus
Case Presentation
A 42-year-old male was admitted to the hospital with a known retained foreign body. A can of shaving cream was inserted into the patient’s rectum several days prior to presentation. On admission, an abdominal radiograph (Figure 1) was taken to confirm the position of the foreign body and the absence of free air in the abdomen. The patient was taken to the operating room and under local anesthesia underwent successful transanal removal of the aerosol can using tenaculum forceps. There was no evidence of bowel perforation. The patient was transferred to the recovery room in stable condition.

Discussion
Insertion of foreign objects into the anus and rectum is a well-described phenomenon. Anorectal objects can be inserted for sexual, medicinal or transportational purposes. They are more common in men than in women. Commonly found rectal foreign bodies may include such objects as vibrators, bottles, fruit, vegetables and toy balls. Some unusual objects reported include a light bulb, a magazine, a pair of spectacles and fish.¹²

The diagnosis of a retained foreign body should be confirmed by a plain abdominal radiograph. It will usually demonstrate a radio-opaque object; however, vegetables and rubber objects may not be visible. Low-lying foreign bodies are distal to the rectosigmoid junction while high-lying foreign bodies are above it. Objects retained within the sigmoid colon frequently require operative intervention.³⁴

Colorectal insertion of foreign bodies may be associated with serious injuries. Delayed removal of rectal foreign bodies can lead to severe complications, including perforation, peritonitis, sepsis, mucosal ulcerations, obstruction and bleeding. Evaluation must include a search for involvement of other structures and an evaluation of the anal sphincter. In treating these patients it is important to recognize previous attempts to remove the object prior to their presentation to the emergency department.² After successful extraction, all patients should be observed to exclude rectal perforation. During that time, psychological support should be provided as well as education to prevent future occurrences.

References
PAINLESS JAUNDICE

When dealing with jaundice that is painless,
Your thinking should not be aimless.

Last night we admitted this fellow,
Whose skin happens to be bright yellow.

Much to his dismay,
His poop looks like clay.

He found it important to remark,
That is pee-pee is very dark.

His AST/ALT and bilirubin are high,
But his alk phos is normal, and we want to know why.

There are many causes with potential,
So let’s begin with the differential.

When you begin your differential construction,
You might want to think about obstruction.

On the list is hemolysis,
Along with hepatic cirrhosis.

To avoid any complications,
First you should go over his medications.

Arising is another question,
Could it be ingestion?

If he drank a lot of booze,
That would be note-worthy news.

Another clue to solve the mystery,
Could be his family and travel history.

But none of this sheds any light
On why he is here tonight.

It didn’t hurt when we palpated his abs,
But let’s talk about some labs.

TSH, CBC, Hepatitis panel, AMA, UDS, CMP—
Let’s find out what’s darkening his pee.

HIV, EBV, Ceruloplasmin, Zoster, HSV—
I think we need abdominal CT.

We will wait to see the results of all the tests
And see what they might suggest.

There is a feeling of dread,
That this may be cancer of the pancreatic head.

But let’s not fly too close to the sun like Icarus,
Just because there is scleral icterus.

Nilay Kavathia, MD

Photograph courtesy of Sandarsh Kancherla, MD
Photograph courtesy of Sandarsh Kancherla, MD
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