As we were completing the final touches on the 8th volume of The Jefferson Medicine Forum, the members of the editing staff could not help but note the vast variety of medicine we are privileged to witness daily. Textbook cases of malaria, herpes zoster ophthalmicus, and Lyme disease mixed among patients with migrating prostatic radiation seeds or reversible encephalophathy due to hypertension are the perfect example of the marvelous diversity of pathology to which we are exposed. Our residents have interests ranging from coronary heart disease to irritable bowel disease and research throughout the spectrum of internal medicine.

Residents are committed to helping those who are ill, to scholarly pursuits within medicine, but are also passionate about photography, art, and poetry.

Thank you to all of our colleagues who shared their experiences in this edition of The Forum and we hope that you enjoy!

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**Inverse Expression of Fas Ligand and Asthma-Related Cytokines in an Aspergillus Challenge Murine Model of Asthma**

T. Lin, MD, Allyson Larkin, MD, S. Sharma, MD, S. Patel, MD, J. Peterson, MD, S. Kierstein, MD, A. Haczku, MD, J. Zangrilli MD

**Introduction**

Resolution of inflammation in asthma is typically thought of as a passive phenomenon in which proinflammatory Th2-type cytokines wane after the initial trigger. We hypothesized that active mechanisms, including anti-inflammatory cytokines and pro-apoptotic factors, contribute to this process. Fas Ligand (FasL) expression was particularly interesting since important effector cells in asthma (e.g. eosinophils and T helper cells) are Fas-sensitive.

**Methods**

BALB/c mice were sensitized and challenged with an Aspergillus fumigatus extract, and sacrificed 1, 7 and 10 days later to capture events during initiation of the inflammatory response and its resolution. Endpoints included bronchoalveolar lavage (BAL) cell counts, protein array analysis of BAL fluid, and cytokine gene array of total lung RNA. Results: BAL eosinophilia peaked on day 1 and was associated with a marked increase in both Th1 and Th2 type cytokines including IL-12, IFN-α, IL-4, IL-5, IL-6, and IL-10 and eosinophil-active chemotactic factors. In contrast, FasL protein and gene expression was suppressed at this time point compared to baseline. Resolving eosinophilia was coincident with a marked increase in FasL expression and the return of most cytokines towards baseline although residual chemokine levels were noted 10 days after allergen challenge.

**Conclusion**

We observed an inverse relationship between expression of FasL and asthma-related cytokines in an experimental asthma model. These data are consistent with a regulatory role for FasL during resolution. While Th2 cytokines are thought to orchestrate the initial response to antigen, multiple classically anti-inflammatory cytokines appear to be involved as well.

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*Photo courtesy of Vaibhav Menendiratta, MD*
**CIDOFOVIR AND INTRAVENOUS IMMUNOGLOBULIN FOR TREATMENT OF BK POLYOMAVIRUS NEPHROPATHY**

Anita Mehrotra, MD, Rajani Dinavahi, MD, and George C. Francos, MD

**Abstract**

BK polyomavirus nephropathy (BKN) is an important cause of renal allograft dysfunction and loss. The mainstay of therapy is reduced immunosuppression, but definitive protocols for the diagnosis and management remain to be defined. We report here a retrospective analysis of 6 patients with BKN treated with cidofovir and intravenous immunoglobulin (IVIG). The patients were followed for 6 months from the initiation of therapy. All patients (3 cadaveric/3 live donors) underwent renal biopsy after serum BK viral PCR (SBKPCR) was obtained in response to a rise in creatinine concentration. The mean time from transplantation to diagnosis was 21.7 months (5, 14, 15, 24, 35, 35 months). One patient had positive SBKPCR without biopsy evidence of BKN. In all patients immunosuppression was reduced, and therapy with cidofovir (0.25-0.5mg/kg) and IVIG (25 grams) was instituted weekly or bi-weekly. Mycophenolate mofetil was discontinued, and the tacrolimus therapeutic trough was decreased to 2-5 ng/mL in 5/6 patients. Therapy was continued for 6 months or until SBKPCR was undetectable. The mean nadir creatinine value after transplantation was 1.3mg/dL (1.1, 1.1, 1.2, 1.3, 1.8). The mean creatinine value at time of biopsy was 2.3 mg/dL (1.2, 1.4, 1.7, 2.8, 3, 3.6), and the mean SBKPCR value at diagnosis was 870, 266 copies/mL (1.86, 23, 33, 38, 56, 370 x 10^4 copies/mL). The average number of cidofovir doses was 8.3 (4, 6.6, 10, 12, 12 doses) with concomitant IVIG. The mean SBKPCR at end of 6 months was 44,283 copies/dL (1.1, 1.8, 2.4, 5.4, 10, 245 x 10^3 copies/mL). Five of 6 patients experienced a decrease in SBKPCR. The mean creatinine value at the end of 6 months was 3.0 mg/dL (1.5, 2, 2.9, 3.3, 3.7, 4.4). After nine months from initiation of therapy, the one patient with positive SBKPCR and biopsy negative for BKN returned to a nadir creatinine (1.2 mg./dL) and undetectable SBKPCR. Baseline renal function (the nadir creatinine prior to the diagnosis of BK infection), was not recovered in any patient at the end of six months. These data suggest that the reduction of immunosuppression and addition of cidofovir and intravenous immunoglobulin can arrest further progression of BKN. Allograft dysfunction, however, was not reversed and may reflect fibrosis secondary to the injury sustained as a result of BKN. The one patient diagnosed by SBKPCR prior to the development of BKN had the most favorable outcome. Serologic screening prior to development of allograft dysfunction may be warranted, but the timing and treatment strategies need to be confirmed by larger studies.

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*Yeongbokgung Palace
Seoul, Korea

Photo courtesy of Eric Choi, MD*
**Irritable bowel syndrome has long been considered a functional gastrointestinal disorder. However, recent studies have suggested possible organic causes that can explain the multitude of symptoms in IBS.**

**Brief History**

The irritable bowel syndrome has been thought of as a functional gastrointestinal disorder for many years. As long as three thousand years ago, Hippocrates described a triad of symptoms consisting of abdominal discomfort, irregular bowel movements and bloating. In 1817, William Powell reported a case with similar symptoms as Hippocrates. In 1849, Cumming described a syndrome of irregular bowel habits consisting of alternating diarrhea and constipation. In 1928, Bockus and his colleagues described the syndrome as “neurogenic mucous colitis.” Bockus determined that this disease can only be diagnosed by exclusion which was the belief until the 1970’s.

**Epidemiology**

Today IBS is one of the most common diagnosed medical problem affecting an estimated 4-35% of the population worldwide, with a prevalence of 9-22% in the United States. Approximately 12% of office visits in the United States are due to IBS along with approximately 28% of gastroenterology referrals. It is the 7th most common outpatient diagnosis. Irritable bowel syndrome is the second most common cause for absenteeism, trailing only the common cold. Disability rates are equal to or more severe than organic GI diseases. The prevalence rate is 2-3 times higher in women. This appears to be the case worldwide except in India and Sri Lanka where there is no known gender differences. Hispanics and Asians are less likely to have IBS. There have been conflicting studies on the prevalence differences for Caucasians versus African Americans. The onset usually is in the late teenage years and twenties. The prevalence peaks in the 3rd and 4th decades and begins to decline in the 6th and 7th decades. After diagnosis, up to 75% of patients will remain symptomatic after 5 years.

**Economics**

IBS patients miss three times as many work days as the average person. In the United States, the disease accounts for 3.5 million office visits, 2.2 million prescriptions and 35,000 hospitalizations per year. Patients with IBS use more medical resources than the non-IBS patient. These include physician visits, tests, unnecessary surgeries and medications. It is currently estimated that IBS costs the United States between 15-30 billion dollars per year. This includes both direct medical costs as well as indirect costs.

**Extraintestinal symptoms**

Patients with IBS undergo more appendectomies and hysterectomies than non-IBS patients. The most common extraintestinal manifestations include genito-urinary symptoms such as dysmenorrhea, dyspareunia, impotence, urinary frequency, as well as feelings of incomplete bladder emptying. IBS also appears to affect the perception of sexual function. Eighty-three percent of IBS patients compared to 16% of non-IBS patients report impaired sexual functioning.

**Diagnosis**

The diagnosis of irritable bowel syndrome was originally made using the Manning criteria: pain eased with defecation, pain associated with change in frequency of bowel movements, pain associated with change in consistency of bowel movements, abdominal distention, tenesmus, and mucous in the stool. In 1992, the Rome criteria for the diagnosis of irritable bowel syndrome was published. In 2000, the Rome II criteria was published (See Table 1). In a study of 98 patients, confirmed to have IBS using a clinicians diagnosis as the gold standard, it was found that the Rome I criteria in the absence of red flags to be 65% sensitive, 100% specific and 100% positive predictive value. The cornerstone of the Rome Criteria is abdominal pain. Without abdominal pain, IBS can not be the diagnosis.

**Table 1. The ROME I Criteria for the diagnosis of IBS was developed in 1992**

<table>
<thead>
<tr>
<th>ROME I Criteria:</th>
<th>Rome 2 Criteria</th>
<th>Red Flags</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence for at least 12 weeks (not necessarily consecutive) in the preceding 12 months of abdominal discomfort or pain that cannot be explained by structural or biochemical abnormalities and at least two of the following</td>
<td>2 or more of the following, at least 25% of occasions or days:</td>
<td>1. Documented weight loss</td>
</tr>
<tr>
<td>1. Pain relieved with defecation</td>
<td>1. Altered stool frequency</td>
<td>2. Nocturnal Symptoms</td>
</tr>
<tr>
<td>2. Change in the frequency of bowel movements</td>
<td>2. Altered stool forms</td>
<td>3. Blood mixed in the stool</td>
</tr>
<tr>
<td>3. Change in the form of the stool</td>
<td>3. Altered stool passage</td>
<td>4. Recent antibiotic use</td>
</tr>
<tr>
<td>4. Bloating or feeling abdominal distention</td>
<td>4. Relevant abnormalities on physical exam (2)</td>
<td>5. Family history of colon cancer</td>
</tr>
</tbody>
</table>

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Gender and Hormones
Hormones appear to play a role in IBS. The symptoms appear to be worse in women during menstruation. Women on hormone replacement therapy tend to be more symptomatic than women not on therapy. One study found that men with IBS are more likely to have lower testosterone and luteinizing hormone than unaffected men. Other studies have found that men with IBS have more nurturing traits and reduction in the male-trait score.

Psychological Factor and Abuse
A history of abuse predisposes patients to IBS. In addition to having a history of abuse of varying types; emotional, sexual, or physical and/or a history of stressful life events, social stress or anxiety and having a maladaptive coping style, affect the severity and clinical course of IBS. There is a strong association between IBS and having a concurrent psychological disturbance. Various studies have demonstrated a 40-90 percent association rate with IBS. Psychological disorders associated with IBS include personality disorders, psychological distress, altered health beliefs and coping styles.

Infection
Researchers have suggested that IBS can be explained by bacterial overgrowth in the small intestines. The theory stems from the finding that regardless of the predominant symptom of IBS, 92% of the patients complain of abdominal bloating. The bloating is usually postprandial. Numerous imaging studies show increased intestinal gas in IBS patients. Total hydrogen gas excretion and the maximal rate of gas excretion following lactulose ingestion was higher in IBS patients. The gases produced are hydrogen and methane which demonstrates that this abnormal gas production following lactulose intake in IBS patients cannot be explained by simply a disaccharide intolerance.

Normally, it is uncommon for bacteria to grow in the proximal small intestine. It has been theorized that there is a proximal spread of bacteria along the small intestines. New bacterial growth in the proximal small intestine may be the cause of the increased gas production in IBS patients. Nucera et al found that out of 200 patients with IBS, 75 percent had abnormal lactulose-glucose breath tests. This is consistent with bacterial overgrowth of the small intestine.

Another study found that 78% of IBS patients had an abnormal breath test. This suggested that a small intestine bacterial overgrowth may be present. The study consisted of 202 IBS patients who had met the Rome I Criteria. They were treated with antibiotics with successful eradication of the bacteria being measured by a normal breath test. After eradication, half of the patients no longer met the Rome I Criteria. This study was followed with a double-blind randomized control trial. This follow-up study consisted of 111 patients with IBS. Thirty-seven percent of those with IBS had normalization of global symptoms within one week compared to just 11% in placebo-treated patients. Of the patients who bacterial eradication was considered complete, 75 percent achieved normalization of global symptoms. Another study proved that metronidazole is superior to placebo in alleviating symptoms in IBS. This is further evidence of bacterial overgrowth as the potential etiology in at least some IBS patients.

In recent years, studies have shown that a high percentage of people with infectious gastroenteritis develop IBS. This was demonstrated in two control studies. The first study followed 318 subjects with gastroenteritis and compared them to a population database of 584,308 controls for one year to see if a diagnosis of IBS was made. They found that 4% of the post-infectious patients had developed IBS within 12 months compared to 0.3% of the general population. A second study followed post-infectious gastroenteritis subjects and controls for 6 months and found that 17% had developed IBS compared to only 1.9% of the controls. The odds ratio was 10 (95% confidence interval, 3-31). This study used the Rome II criteria for diagnosis of IBS. Overall, the incidence of post-infectious onset IBS has been shown to be between 4-30%.

Inflammation
Several studies have shown the presence of increased inflammatory cell levels in patients with IBS. These findings include increased mast cells in the muscularis externa of the colon and ileum, increased cellularity of the colonic and ileal mucosa, lymphocytic infiltrates in the myenteric plexus and increased nitrous oxide synthetase. The findings of inflammation occur usually within three months of infectious gastroenteritis. During this time period, IBS patients have a higher lymphocyte count in the rectal mucosa. The count is not high enough to meet the criteria for lymphocytic colitis. A small study of patients with severe IBS have shown that on full thickness biopsy, a low grade ganglionitis existed. Two of the ten IBS patients with the low grade ganglionitis had post-infectious IBS. There is also evidence that low grade inflammation of the small intestine such as the inflammation following Campylobacter infection could cause bile acid malabsorption. In turn this could cause the symptoms of post-infectious IBS.

Enteric nervous system
One of the earliest studies to show that the nervous system played an important role in IBS involved the difference in perception of pain in patients with IBS compared to controls. Ritchie found that patients with IBS experienced rectal pain when a balloon was inflated in the rectum at lower volumes than non-IBS patients. In this study, fewer than 10% of non-IBS subjects reported pain at a distending volume of about 60 ml compared to greater than 50% of IBS patients reporting pain at the same distending volume. The enteric nervous system (ENS) is a complex system that rivals the spinal cord and brain in the number of nerves and neurotransmitters involved. It can work both in conjunction with the CNS as
well as on its own as demonstrated in pig intestines in vitro. Intrinsic primary afferent neurons (IPAN) are analogous to dorsal root ganglia of the CNS. They are the peripheral sensors that feed information to the ENS in order to allow autonomous regulation of the gut by the ENS. Drugs that activate IPANs stimulate diarrhea and drugs that inhibit their action cause constipation. One clinical trial used 5-Hydroxyindalpin to stimulate the IPANs and the result was diarrhea. It has been theorized, however, that a drug that targets the distal terminal of IPANs may lead to better control of gut motility. When stimulated by 5HT-4, IPANs cause the release of acetylcholine and calcitonin g related peptide. These neurotransmitters induce gut motility. 5HT-4 also causes the increase release of 5HT-4 at neuromuscular junctions and nerve-nerve synapses in the myenteric plexus. The combination of these factors is the reason that Tegaserod, a 5HT-4 receptor agonist, stimulates gut motility. Tegaserod has been shown to provide relief of IBS-c (constipation type) over placebo in several trials. 5HT-3 is the signal used by the CNS to interpret the intestinal tract environment. Like 5HT-4, 5HT-3 is part of the prokinetic pathway. Antagonizing 5HT-3 is useful in the treatment of hypermotility states such as IBS-D (diarrhea type). Alosetron and Cilansetron, 5HT-3 antagonists, have been effective in the treatment of IBS-D.

Celiac Disease

Celiac disease and irritable bowel syndrome share many common gastrointestinal symptoms. It was found that patients with irritable bowel syndrome as diagnosed by ROME II criteria have a higher association with also having celiac disease as compared to normal controls. One study tested for the presence of celiac disease by the presence of serum IgA antigliadin, IgG antigliadin, and endomysial antibodies in 300 patients diagnosed with IBS. Positive antibody tests were followed by biopsy for confirmation of the diagnosis. The results were compared to 300 patients who did not carry the diagnosis of IBS. They found that 14 patients with IBS also had celiac disease compared to just 2 of the non-IBS controls (p=0.004, odds ratio = 7.0 [95% CI 1.7-28]). According to this study, it may be prudent to refer patients with IBS for Celiac disease testing.

Another smaller study comparing 34 subjects with dyspepsia, 50 subjects with IBS, and 78 asymptomatic healthy controls did not show a statistically significant difference in the association with celiac disease. However, in this study celiac disease was diagnosed solely by serology. Whether there is an actual association between the diseases or merely celiac patients falsely being labeled with IBS remains to be seen. Future studies should look into the results of treating the celiac disease to see if the IBS symptoms remain.

Diagnosis

Until recently, the diagnosis of IBS was a diagnosis of exclusion which required a lengthy battery of tests. With the advent of the Rome criteria, physicians have been able to make the diagnosis of IBS on the basis of symptoms in the absence of red flags. Several studies examined the pre-test probability and prevalence of organic disease in patients with IBS. Using flexible sigmoidoscopy, colonoscopy, and barium enema, between 0-1.3% of patients were found to have organic disease. Other studies using abdominal ultrasonography and rectal biopsy failed to identify organic disease in IBS patients. Laboratory studies such as a complete blood count, chemistry panel and fecal occult blood testing similarly found organic disease in only 0 to 1.3% of IBS patients. TSH was abnormal in 0.6 to 6% of patients. Several studies have shown that IBS patients have abnormal breath tests for lactose intolerance in 22-26% of cases. However, one study found the presence of an abnormal breath test in 78% of IBS patients. In addition, Celiac disease was found to be more prevalent in IBS patients, 5% compared to 1% of the general population.

The alarms or red flags (see Table 1) used in the Rome criteria such as hematochezia, anemia, weight loss, chronic severe diarrhea and family history of colon cancer, all lead to a high pre-test probability of organic disease and therefore justify initiating a targeted work-up. The Rome I criteria was found to be 65% sensitive, 100% specific with a 100% predictive value for IBS.

Treatment

The etiology of IBS is complex with overlapping etiologies contributing to the symptoms. (See Figure 1) It has been proposed that small bowel bacterial overgrowth, post-infectious states, inflammatory states as well as psychological factors, all contribute to the vast symptoms of IBS. For this reason, the treatment must be tailored to each IBS patient. Patients with predominant psychological etiology may do well with antidepressants and behavioral therapy. Several studies have looked into treating patients with antibiotics when bacterial overgrowth is the suspected etiology. Other therapies are used to control symptoms such as antispasmodics, bulking agents, and serotonin receptor agonists and antagonists.

Antispasmodics

There are two antispasmodics available in the United States, dicyclomine and hyoscyamine. These drugs are thought to work by decreasing the spontaneous activity of the intestinal smooth muscles. Atropine-like adverse effects often lead to intolerance and the relaxation of the smooth muscle can worsen constipation. Currently there is only a grade B recommendation for the use of anti-spasmodic agents for IBS management. Five smooth muscle relaxants were found to have greater efficacy than placebo. These include cimetropium bromide, pinaverium bromide, octylonium bromide, trimebutine, and mebeverine.

Bulking agents

Several bulking agents have been studied including wheat, bran, corn, fiber, calcium, polycarbophil, ispaghula husk and psyllium. Bulking agents were effective in improving stool bulk and stool frequency but they were not found to be more effective than placebo. Adverse effects of bloating and abdominal discomfort were worsened by those agents.
Anti-diarrheal agents
Diarrhea can be controlled with many over the counter agents such as Loperamide which includes Immodium and Kapectate II among others. This agent works by slowing gut transit and up regulating water and electrolyte absorption. Prescription Lomotil can be used if the over the counter agents fail to provide relief.

Serotonin receptor agonist (5HT4)
Serotonin receptor activation stimulates peristalsis thereby increasing intestinal and colonic transit time and also reduces visceral sensitivity. Tegaserod is the only 5HT4 currently available. Several well-designed, randomized, controlled trials using the ROME criteria for diagnosis have demonstrated significant improvement of constipation symptoms. The recommended dosage is 6mg twice daily and the trials duration extended over 12 weeks. Significant reduction of bloating, abdominal discomfort and improvement of bowel-habit satisfaction were reported but the magnitude of these improvements were not consistent among those trials. This is likely secondary to different methodology used to evaluate the symptoms. 9-10% of patients reported diarrhea as the most frequent adverse effects compared to 4-5% in the placebo group. Another recent study looking at the efficacy of Tegaserod for repeated therapy using 2660 patients found that Tegaserod was superior to placebo in both initial use and repeated therapy. It should be kept in mind that the FDA approved regimen is only for short duration in females whose primary symptom is constipation. The role of Tegaserod is not clearly defined in patients with alternating constipation with diarrhea. No recommendation exists for males.

Serotonin receptor antagonist 5HT3
5HT3 antagonism slows colonic transit and improves discomfort. Alopsetron has a grade A recommendation by the ACG for IBS with diarrhea. The most commonly reported adverse effect is constipation occurring in 22-39% of patients vs 3-14% controls. Unfortunately, ischemic colitis is unpredictable. Physicians are advised to adhere the FDA guideline of using Alopsetron for “women with severe, diarrhea-predominant IBS who failed to respond to conventional IBS therapy” in view of the potentially serious adverse effects.

Behavioral and psychotropic therapy
Because of the frequent findings of psychological disorders in IBS, especially depression and anxiety disorders, behavioral therapies have been tried for treatment. There have been at least 16 randomized controlled trials. Presence of a psychological disorder was found in 80% of patients. Unfortunately, these trials contained flaws in the methodology. Behavioral therapy seems to improve both the IBS symptoms and the psychological manifestations although the evidence fails to be unequivocal. Currently, only behavioral therapy has Grade A recommendation for the treatment of IBS.

The use of antidepressants has been helpful in some patients. Those with abdominal pain, bloating and diarrhea seem to be most susceptible to the benefits of tricyclic antidepressants. The mechanism of action is two-fold. First, they appear to effect motility and visceral sensitivity as well as central pain perception. They also have anticholinergic effects which can help with diarrhea. More recent studies have found SSRIs to be somewhat helpful in alleviating symptoms and improving mood.

Hypnotherapy
Several studies have evaluated the benefit of hypnotherapy in reducing symptoms of IBS in both the short and long-term. One study consisted of IBS patients receiving weekly 1-hour session of gut-directed hypnotherapy for a total of 12 weeks. They found that the patients improved in the long-term follow-ups. Another study followed 204 patients using questionnaires for 6 years. They

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**Figure 1:** Diagram demonstrating the proposed overlapping etiologies of IBS.

**Figure 2:** Algorithm for evaluation and treatment of IBS.
found that initially 71% of the patients had symptom improvement. After 5 years, only 19% of the patients who initially responded had regressed. Measures of quality of life, anxiety, and depression all were statistically significantly improved.57

Future therapy
There is overwhelming evidence that small bowel bacterial overgrowth is prevalent in a much higher percentage of patients with IBS compared to the healthy population. There is current research looking into an algorithm for treating IBS according to this data. The algorithm calls for a lactulose breath test at the time of initial patient presentation. If the breath test is positive, treatment with Cipro/Flagyl have been successful in eradicating bacterial overgrowth, resulting in a negative breath test.25,26 Following bacterial eradication, patients can then be started on traditional therapy for IBS up to and including the 5HTa agonists and antagonists. We are currently studying the efficacy of Xifaxan 400 mg TID and comparing it to Cipro or Flagyl for use in bacterial eradication in the small bowel. It is our opinion that small bowel bacterial overgrowth is not the only etiology of IBS but one of many triggers.

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CORONARY HEART DISEASE PREDICTION AND PREVENTION

Dae Hyun Kim, MD, MPH, Andrew N. Lee, MD

Introduction
Prediction of coronary heart disease (CHD) is based on multivariable risk equations developed from population-based observational studies in which people without clinical CHD at the initiation of study were examined and followed until their first CHD events. The risk equations from the Framingham Heart Study have been widely used in our clinical practice and research. The recent report of the third National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) incorporated the Framingham risk equations to predict ten-year absolute CHD risk and to identify certain patients who are at high risk and more likely to benefit from primary prevention with aggressive lipid-lowering treatment. In addition to CHD prediction, population-based observational studies also provide the clue to understand how much of CHD can be prevented by modifying major cardiovascular risk factors such as serum cholesterol level, blood pressure level, and current smoking.

In this narrative review, we described how CHD prediction works and how it can be improved by including nontraditional cardiovascular risk factors. We also discussed about how likely it is to prevent the majority of CHD.

How Do We Predict CHD?
The Framingham Heart Study has developed mathematical functions to assess the relative importance of CHD risk factors and to quantify absolute CHD risk for individual patients. Detailed methods of derivation of CHD risk equations were described elsewhere. Briefly, sex-specific CHD risk equations were derived from a population-based sample of 2489 men and 2856 women, 30 to 74 years of age, who were free of overt cardiovascular disease at the time of their 11th examination of the original Framingham Cohort or the initial examination of the Framingham Offspring Study in 1971 to 1974. CHD risk factors were routinely and systematically measured during these examinations and twelve-year follow-up was obtained for the development of “hard” CHD events, defined as myocardial infarction and CHD death. Sex-specific Cox proportional hazards regression was performed to calculate the relative importance of CHD risk factors using age, current smoking, presence of diabetes, the fifth Joint National Committee on Hypertension blood pressure categories, and the second NCEP-ATP cholesterol categories as covariates. (Table 1) In addition, score sheets were developed from the beta-coefficients of Cox proportional hazards models to provide ten-year absolute CHD risk and to make it easy to implement as part of a screening program. They were adopted by the NCEP-ATP III guideline. The predictive capability of the model using a continuous variable or a categorical variable for cholesterol level was almost identical. The equation is particularly useful when there are multiple mild abnormalities that increase CHD risk synergistically.

In the Framingham risk equation, several candidate risk factors such as family history of CHD, elevated fibrinogen levels, left ventricular hypertrophy on the electrocardiogram, postmenopausal estrogen replacement therapy, physical activity, high serum triglyceride, and body mass index, were not included for practical reasons, although they may contribute to the risk of CHD.

How Well Does CHD Prediction Equation Work?
The performance of the CHD risk prediction models has been examined according to discrimination and calibration. From the coefficients of the prediction model, a risk score can be calculated for each person by multiplying the person’s risk factor level by the associated coefficient for that risk variable, then summing all these products. Those with a higher risk score from a prediction model are expected to have higher CHD events. Discrimination is the ability of a predictive model to separate those who experience hard CHD events from those who do not. It can be quantified by c-statistic or the area under a receiver operating characteristic (ROC) curve (AUC) which indicates the probability that a person who had an incident CHD event within a specified time had a higher risk score than a person who did not have an event by that time. The AUC has a range between 0.5 and 1. When the variables in the prediction model are unrelated to the event, the expected AUC would be 0.5. The greater the AUC is, the better the prediction model works. Calibration, another measure of performance of the prediction model, measures how closely predicted outcomes agree with actual outcomes.

Table 1. Multivariate-Adjusted Relative Risks (RR) for CHD from the Framingham Heart Study: Twelve-Year Follow-Up of 2489 Men and 2856 Women (Adapted from Wilson et al)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Normal</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>High Normal</td>
<td>1.32</td>
<td>0.98-1.78</td>
</tr>
<tr>
<td>Hypertension Stage I</td>
<td>1.73‡</td>
<td>1.32-2.26</td>
</tr>
<tr>
<td>Hypertension Stage II</td>
<td>1.92‡</td>
<td>1.42-2.59</td>
</tr>
<tr>
<td>Cigarette Use [Yes/No]</td>
<td>1.71‡</td>
<td>1.39-2.10</td>
</tr>
<tr>
<td>Diabetes [Yes/No]</td>
<td>1.47*</td>
<td>1.04-2.08</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;130</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>130-159</td>
<td>1.19</td>
<td>0.91-1.54</td>
</tr>
<tr>
<td>≥160</td>
<td>1.74‡</td>
<td>1.36-2.24</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>1.46‡</td>
<td>1.15-1.85</td>
</tr>
<tr>
<td>35-59</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>≥60</td>
<td>0.61*</td>
<td>0.41-0.91</td>
</tr>
</tbody>
</table>

* 0.01 < P < 0.05, † 0.001 < P < 0.01, ‡ P < 0.001.
Since the Framingham risk equation was derived from a community sample of white middle-class individuals from a suburb of Boston, concerns have existed regarding its generalizability to other populations. To test the validity, the sex-specific Framingham risk equations were applied to six prospectively studied, ethnically diverse cohorts including the Atherosclerosis Risk in Communities Study (ARIC), Physicians' Health Study, Honolulu Heart Program, Puerto Rico Heart Health Program, Strong Heart Study, and the Cardiovascular Health Study. The performance of the prediction equation was compared using discrimination and calibration. For white men and women, the Framingham risk equations performed reasonably well within five years of follow-up (Figure 2). Among Japanese American and Hispanic men and Native American women, the equation overestimated the risk. However, after taking into account different prevalence of risk factors and underlying CHD rates, it performed well in these populations.

Then, how much of incident CHD events are explained by known risk factors? The CHD prediction equations have been used to answer this question. In the Seven Countries Study, the prediction equation using systolic blood pressure, cholesterol, smoking, and age derived from the US railroad workers was applied to men in

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**Figure 1. Score Sheets for Estimation of Ten-Year CHD Risk for Men and Women (Adapted from NCEP-ATP III Guideline)**

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**Table B1. Estimate of 10-Year Risk for Men**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-74</td>
<td>4</td>
</tr>
<tr>
<td>55-59</td>
<td>6</td>
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<tr>
<td>50-54</td>
<td>8</td>
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<td>45-49</td>
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<td>40-44</td>
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<tr>
<td>35-39</td>
<td>14</td>
</tr>
<tr>
<td>30-34</td>
<td>16</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Cholesterol, mg/dL</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>0</td>
</tr>
<tr>
<td>150-199</td>
<td>4</td>
</tr>
<tr>
<td>200-239</td>
<td>7</td>
</tr>
<tr>
<td>240-279</td>
<td>9</td>
</tr>
<tr>
<td>&gt;279</td>
<td>11</td>
</tr>
</tbody>
</table>

---

**Table B2. Estimate of 10-Year Risk for Women**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-74</td>
<td>5</td>
</tr>
<tr>
<td>55-59</td>
<td>7</td>
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<tr>
<td>50-54</td>
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<td>45-49</td>
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<td>35-39</td>
<td>15</td>
</tr>
<tr>
<td>30-34</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Cholesterol, mg/dL</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
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<tr>
<td>200-239</td>
<td>7</td>
</tr>
<tr>
<td>240-279</td>
<td>9</td>
</tr>
<tr>
<td>&gt;279</td>
<td>11</td>
</tr>
</tbody>
</table>

---

**Figure 2. Performance of Framingham Predictive Risk Equations in Various Populations**

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Since the Framingham risk equation was derived from a community sample of white middle-class individuals from a suburb of Boston, concerns have existed regarding its generalizability to other populations. To test the validity, the sex-specific Framingham risk equations were applied to six prospectively studied, ethnically diverse cohorts including the Atherosclerosis Risk in Communities Study (ARIC), Physicians' Health Study, Honolulu Heart Program, Puerto Rico Heart Health Program, Strong Heart Study, and the Cardiovascular Health Study. The performance of the prediction equation was compared using discrimination and calibration. For white men and women, the Framingham risk equations performed reasonably well within five years of follow-up (Figure 2). Among Japanese American and Hispanic men and Native American women, the equation overestimated the risk. However, after taking into account different prevalence of risk factors and underlying CHD rates, it performed well in these populations.

Then, how much of incident CHD events are explained by known risk factors? The CHD prediction equations have been used to answer this question. In the Seven Countries Study, the prediction equation using systolic blood pressure, cholesterol, smoking, and age derived from the US railroad workers was applied to men in
fifty European countries.\(^{11}\) Fifty one percent of CHD events occurred in top quintile of the predicted CHD risk. Based on this finding, it is often said that only 50 percent of the CHD is explained by the known risk factors. In another study, the Framingham equation was applied to the National Health and Nutrition Examination Survey I, a probability sample of the US population.\(^{12}\) Thirty nine percent of CHD deaths in men and 59 percent in women occurred in top quintile of the predicted risk. Based on these findings, can we say that approximately 40 to 60 percent of CHD mortality is due to known causes and the remaining percent is due to unknown causes? This is a very common misinterpretation. Counting cases attributable to the upper end of the risk distribution defined by an arbitrarily high cut point on the scale is misleading, because most of the risk factors have a continuous graded relationship to risk.\(^{13}\)

In a study using five large cohorts of young and middle-aged adults in the Multiple Risk Factor Intervention Trial (MRFIT) and Chicago Heart Association Detection Project in Industry (CHA) who were free of diabetes and myocardial infarction, low-risk participants who had cholesterol level less than 200 mg/dL, blood pressure less than or equal to 120/80 mmHg, and no current smoking, experienced significantly and markedly lower CHD death rates by 77 to 92 percent than the rest of the cohorts during the mean follow-up period of 16 years for MRFIT and 22 years for CHA.\(^{14}\) This suggests that three major risk factors – serum cholesterol level, blood pressure, and smoking – account for the majority of CHD death. Similar results were found in the ARIC study.\(^{15}\) Not being in the bottom decile of risk score derived from traditional risk factors accounted for 72-75 percent of CHD risk in men and 89-93 percent in women. Evidences from numerous cohort studies with long follow-up have shown that the major established risk factors explain at least 75 percent of the CHD events within populations and there is no evidence supporting the only-50-percent claim.

Can We Improve CHD Risk Equation?
If traditional risk factors in the Framingham risk equation – total cholesterol, HDL cholesterol, current smoking, diabetes, and blood pressure – can explain 75 percent of incident CHD events, how can the remaining 25 percent be explained? Investigators in the ARIC study examined the improvement in the predictive capability of the basic risk equation by adding the following nontraditional risk factors: body mass index, waist-hip ratio, Keys score, albumin, white blood cell count, “residual” forced expiratory volume at 1 second (FEV1) (calculated as the difference between measured FEV1 and the predicted FEV1 from age, height, and sex), fibrinogen, factor VII, von Willebrand Factor, lipoprotein(a), heart rate, pack years cigarette smoking, sport activity index, and creatinine.\(^{16}\) Among the nontraditional risk factors considered, no single factor provided a large improvement in predictive capability of the basic equations only including total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medications, current smoking, and diabetes. When nontraditional risk factors and intima-media thickness were added to the basic model, the predictive capacity of the model was significantly improved, as measured by the gain in the AUC above the 0.5. (Table 2)

**Have We Reached the Limits in CHD Prediction?**
In the ARIC study, 531 CHD events occurred among 4287 white men during ten years of follow-up period since the baseline examination in 1987.\(^{17}\) If we were able to predict CHD perfectly, we could identify those 531 high-risk men at baseline: 100 percent of them should develop CHD events within ten years and none of the remaining 3756 low-risk men would have events. This is theoretically impossible because the CHD risk exists in continuum in a population. Some practical limitations also exist. The CHD events can be unrecognized because of silent myocardial infarction, microinfarction, or unwitnessed deaths. Sometimes deaths are falsely attributed to CHD. In addition, true CHD risk may relate more closely to lifetime cholesterol level or blood pressure level rather than their levels measured at one point or during a relatively short period. Blood tests may not precisely measure atherosclerotic or thrombogenic processes. There is always a possibility of unmeasured or undiscovered risk factors as well. Even if the science were complete, there still exists a source of variation from random effects. For these reasons, we will never be able to predict CHD perfectly.

If research since 1979 has improved overall prediction so little, have we discovered all the important risk factors? Is there any evidence that we could predict CHD events better? Some indirect historical evidences suggest that there is more to be discovered. In William Osler’s lecture to Royal College of Physicians in 1910,\(^{18}\) the number of angina cases per hospital admissions was approximately 1 case per year in large hospitals. In his perspectives,\(^{19}\) Paul Dudley White, a graduate of Harvard Medical School in 1911 and founding member of the American Heart Association and International Council of Cardiology, described that there were very few angina cases after review of his voluminous notes

### Table 2. Area Under the ROC Curves Comparing Basic and Full Models (Adapted and modified from Chambless et al\(^ {1})\)

<table>
<thead>
<tr>
<th>Model</th>
<th>Black Women</th>
<th>White Women</th>
<th>Black Men</th>
<th>White Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic†</td>
<td>0.830</td>
<td>0.793</td>
<td>0.669</td>
<td>0.685</td>
</tr>
<tr>
<td>Full‡</td>
<td>0.845</td>
<td>0.805</td>
<td>0.720</td>
<td>0.733</td>
</tr>
</tbody>
</table>

* N indicates sample size and n indicates the number of CHD events.
† Basic model included total cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medications, current smoking, and diabetes.
‡ Full model included body mass index, waist-hip ratio, Keys score, albumin, residual FEV1, fibrinogen, factor VII, von Willebrand Factor, lipoprotein(a), heart rate, pack years cigarette smoking, sport activity index, and intima-media thickness.
during his medical internship at the Massachusetts General Hospital from 1912 to 1913. Among his 100 publications in his early career between 1913 and 1926, there were only two papers related to CHD. According to these evidences, CHD may have been a rare disease in 1910. However, problems exist with historical evidences: they were mainly personal observations and there are major concerns about diagnostic accuracy such as the unavailability of electrocardiogram or cardiac enzyme tests. It is also possible that people did not live long enough to develop CHD.

Besides historical evidences, ecological evidences provide an opportunity to examine the different characteristics and their potential contribution to incident CHD events among populations in different geographic locations. In the International Atherosclerosis Project18 where 21302 autopsies from 15 geographic locations and four race-sex groups were assessed, the age-adjusted percent of intimal surface of coronary arteries involved with raised atherosclerotic lesions varied up to three folds from 6 percent in Durban Bantu or Guatemala to 18 percent in New Orleans whites and Oslo. Prevalence of coronary stenosis among those aged 45 to 54 years also varied from 0 percent in Durban Bantu to 20 percent in New Orleans whites. Another autopsy study compared the prevalence of myocardial infarction between African Americans and Africans in Nigeria and between Asian Americans and Asians in Japan and Korea.19 The authors concluded that very low prevalence of myocardial infarction in Africa and Asia was due to environment, not genetics. In a study comparing CHD incidence in men aged 45 to 64 years who participated in three large National Heart Lung Blood Institute-supported cohort studies in the 1960s, the incidence of CHD in Honolulu Japanese and Puerto Rico men was only 40 percent of that observed in the Framingham Heart Study.20 It was suggested that lower levels of risk factors during early lifetime might be responsible for lower CHD incidence. In the Seven Countries Study, ten-year CHD mortality in 16 cohorts was strongly associated with median serum cholesterol levels and the incidence of CHD mortality in low-rate cohorts was 11 percent of that in high-rate cohorts.21 Similar findings between serum cholesterol level and CHD mortality were observed in other studies.7,22 Estimated CHD reduction effect of lowering cholesterol by 0.6mmol (23.2 mg/dL) was 27 percent in cohort studies and 38% percent in ecological studies.7 Like historical evidences, ecologic evidences are not free from limitations: interpretation may be
affected by possible genetic difference. In addition, secular changes in many populations have diminished research opportunities. Despite abovementioned limitations, both historical and ecological evidences suggest that some human adult populations have extremely low CHD event rates and provide a unique perspective to better understand the incidence of CHD events.

Is It Possible to Prevent 90 Percent of CHD Events?

Historical and ecological comparisons have suggested the potential for preventing a large proportion of CHD events in contemporary western countries. It may be possible to prevent 90 percent of CHD events by reducing standard risk factors to optimal levels. In the MRFIT and CHA studies, young non-smoking men with cholesterol level less than 200 mg/dL and blood pressure less than or equal to 120/80 mmHg had 86 to 92 percent less CHD events than the rest of male participants. Similar results were observed in the ARIC study. The benefit from low risk profile was greater for individuals with persisting low risk profile. These studies are prospectively conducted and their estimates are unbiased. Is it feasible for high-risk individuals to reduce their risk to optimal levels? A meta-analysis of risk factor associations with CHD showed that a given change in a risk factor reduces the risk of CHD by a constant proportion of the existing risk regardless of the starting level of the existing risk. (Figure 3) The authors also emphasized that individuals should be selected for preventive treatment only based on a person's absolute risk level and high-risk individuals should receive interventions to modify all reversible risk factors simultaneously. With good motivation from high-risk individuals and aggressive strategies against multiple modifiable risk factors, we may be able to achieve large risk reduction. Then, we can ask whether entire populations can reduce their risk to optimal levels. When the exposure to a risk factor is homogeneous within a population, the case-control and cohort methods will fail to detect

Figure 3. Incidence of CHD According to Diastolic Blood Pressure, Serum Cholesterol, and Body Mass Index (Adapted from Law et al.)

Data were obtained from cohort studies. Incidence was plotted on arithmetic scale (left hand plots) and logarithmic scale (right hand plots).
the risk factor as a cause of an outcome. As a result, the approach aiming at high-risk individuals without a population approach will only protect susceptible individuals, but will not control the causes of incidence in the population.25 According to population-based studies,4,6 more than 90 percent has higher than optimal risk levels. People at less than highest risk are less motivated to change their risk levels and interventions have lower benefit to risk ratios. Therefore, a population strategy is essential for substantial effect.26 There is also evidence that today's average levels of risk factors should not be considered normal.21 When risk factor levels in our ancestors were estimated through studies of isolated communities with a hunter-gatherer lifestyle typical of the Stone Age, the rise in risk factor levels that is currently seen in Western populations did not occur in hunter-gatherer communities and the shift in the Western distributions made current averages high in relation to the prehistoric values. (Table 3) Moreover, lowering all risk factors to optimal levels might not be necessary to prevent the majority of CHD, because even low-risk populations did not have optimal levels of all risk factors. In the Seven Countries Study, the population in Crete had average blood pressure of 134/80 mmHg and 57 percent of smokers and the population in Japan had average blood pressure of 130/72 mmHg and 75% of smokers.21 It seems that very low cholesterol level itself may suffice.

There are evidences supporting the importance of risk factor levels during early life. The Ni-Hon-San study24 suggested early life risk factors may play “predominant role” and geographical comparisons showed that low serum cholesterol level was associated with lower CHD rate than that estimated from within-country cohort studies.7,24 This emphasizes the need for population strategies to alter lifetime risk factor levels. Lifetime low cholesterol levels can be achieved through early dietary modification such as Mediterranean and low-saturated fat diets.

Prevention of CHD can be improved by new risk factor discoveries. Major areas of investigation include inflammation, lipoprotein oxidation, vulnerable atherosclerotic plaque, hemostasis, endothelial vasoprotection, and microvascular disease. Even though they improve the CHD prediction only slightly, their preventive potential may be large. In addition, markers of critical processes may be targets of primary or secondary prevention.

Conclusions
Coronary heart disease is not an inevitable consequence of aging. Major established risk factors can explain 75 to 90 percent of the incidence of coronary heart disease within populations. If the entire population could reduce known risk factor levels to 1st decile, up to 90 percent prevention might be achieved.

If persistent low cholesterol levels can be achieved by population strategies affecting childhood, it alone might achieve 90 percent prevention when the children become adults.

Although nontraditional risk factors add little to overall risk prediction, they might provide effective prevention opportunities.

References
HERPES ZOSTER OPHTHALMICUS WITH THIRD NERVE PALSY
Bonnie Callahan, MD, Utpal Sagar, MD, and Ted Martynowicz, DO

Introduction
Herpes zoster is a recurrent infection of the varicella-zoster virus. When it infects the periorbital region, the virus often involves the ocular structures, and may lead to more disastrous sequelae, including blindness. Despite advancements, including immunization and antiviral therapy, zoster ophthalmicus persists in the population. Therapy mitigates, but does not obviate, many of the complications of infection. Our paper describes a patient with herpes zoster ophthalmicus that presented from the community.

Case Presentation
The patient is an 85 year-old male with a past medical history of HTN, BPH, and open-angle glaucoma who was in his usual state of health until approximately two weeks prior to admission, when he began having episodes of nausea and emesis. A few days later, the nausea and emesis resolved, and he developed rhinorrhea. The next day, he noticed a series of “scabby,” non-painful sores on the left side of his nose. At that time he also noted an intermittent stabbing headache in the area of his left eye and a yellowish, purulent discharge from his left eye with left eye swelling. He was unable to voluntarily open his left eyelid. Vision was preserved in the left eye. Five days prior to presentation he saw his primary care physician who prescribed a regimen of antihistamine, levofloxacin, and ketorolac eye drops. However, his nose lesions and eye swelling worsened, and he then visited an ophthalmologist on the day of presentation to the hospital. The ophthalmologist’s exam revealed elevated intraocular pressure and possible anterior chamber involvement.

On admission he reported no facial trauma and no recent sick contacts. He also denied any headache or eye pain in the last few days. He did report continuing eye discharge and inability to voluntarily open his left eye. Further review of the patient’s past medical history was significant for a history of rectal carcinoma, prostate cancer, hyperlipidemia, bronchitis, chickenpox as a child, and prior basal cell carcinoma of his left eye. Surgical history included a skin cancer removal and “prostate surgery.” Patient reported no known medication allergies. His outpatient medications were felodipine, simvastatin, and finasteride. He was not taking any over-the-counter or herbal medications. Social history was negative for tobacco, alcohol, or substance abuse. He lives with his wife with no pets. He is an army veteran of World War II and is currently retired. He reported no recent travel or occupational exposures. On review of systems, he reported no fever, chills, genitourinary, or musculoskeletal complaints. On exam, he appeared to be in no acute distress. His temperature was 99.8°F, his heart rate 80 beats per minute, his blood pressure 142/76 mmHg, and respiratory rate 20. He appeared comfortable. Head was atraumatic, however his left periorbital region was swollen and mildly erythematous, and the patient, despite encouragement, was unable to open his eyelid voluntarily. Upon raising the eyelid on exam, the patient had purulent discharge from the medial canthus, the sclera was minimally injected, and the left pupil was 3.5-4 mm and non-reactive to light. The right pupil was 2.5-3 mm and reactive to light. Visual acuity was preserved bilaterally. Extraocular movements of the right eye were intact, while the left eye could abduct, but could not adduct, elevate, or move downward. The patient had lesions on the left forehead, eyelid, and tip of the nose that were scab-like. They were not painful, nor were they actively bleeding (Figure 1). The remainder of the patient’s physical exam was unremarkable. Admission laboratory work showed that the patient had no leukocytosis or anemia, and aside from a serum potassium of 3.1, laboratory evaluation was normal.

The patient had already failed outpatient presumptive therapy for bacterial conjunctivitis. The dermatomal distribution of his lesions, corresponding to more than one branch of the ophthalmic division of the trigeminal nerve, the cranial nerve III palsy, along with the acuity and the time course of the illness, were consistent with herpes zoster ophthalmicus infection.

Upon admission, brimonidine ophthalmic drops were started to decrease the intraocular pressure in the setting of open-angle glaucoma. Anterior chamber involvement was noted, for which steroid eye drops were started. Systemic antiviral therapy with acyclovir was also initiated. MRI/MRA of the brain was performed and ruled out aneurysm as an etiology of CN III palsy. The day after admission the patient was again seen by ophthalmology, and artificial tears and timolol were added to the patient’s medication regimen for his increased intraocular pressure and history of open-angle glaucoma. The patient did well on the above prescribed course, and was discharged to home with outpatient follow-up four days after initial presentation. Our last report of follow-up was sixteen days after initial presentation to the VAMC, when the patient was noted to have slow improvement. At that time, he was able to raise his eyelid and maintain it voluntarily for increasing periods of time. His visual acuity remained unaffected by the Herpes Zoster Ophthalmicus, and the edema around his eye was noted to be significantly improved at that time.

Discussion
Herpes zoster is an extremely common neurological affliction, which often occurs at least one time in a person’s life. Estimates have placed the incidence at approximately 2.2-7.1 cases per 1000 person-years. Herpes zoster generally occurs in the elderly, and is caused by reactivation of the varicella-zoster virus. Patients are initially infected by age ten, and the presentation is commonly recognized as chickenpox. The virus then becomes latent in sensory ganglia, and later reactivates, spreading via spinal or cranial nerves to a dermatome. Patients thereafter present with the typical unilateral exanthem, and concomitant acute pain due to inflammation of sensory neurons and skin insults.
And, while the frontal branch of the ophthalmic division of the trigeminal nerve almost always is involved, involvement of the nasociliary branch is quite rare. The appearance of skin lesions at the side of the nose, known as Hutchinson's sign, has been considered a prognostic feature for ocular inflammation in patients with acute herpes zoster ophthalmicus.4 (See Figure 2) Our patient presented with complete ptosis and essentially paralysis of the oculomotor nerve, which is particularly rare in herpes zoster ophthalmicus.3 Furthermore, it has been postulated that involvement of cranial nerves other than the trigeminal nerve occurs by secondary vasculitis in the orbital apex, resulting in diplopia.5

Early and immediate therapy with oral acyclovir is the cornerstone of treatment of this disorder, and has been proven to significantly decrease the incidence of negative sequelae of eye disorders. Patients should be evaluated within one week of starting acyclovir. Patients who present with Hutchinson's sign or visual complaints merit referral to an ophthalmologist.5

References

Poem

Fool

They say God protects fools and the innocent
They say God protects the innocent and the souls of children
Unfortunately the years of childhood has passed me
I doubt that God looks upon me as innocent
So I pray to be the fool

God protects the fools
The fools that don’t know any better
Those who live by folly
Those who are compared to, throughout his scripture
Why does God protect those who he mocks throughout his book
The fool in the book of wisdom is the enemy
The fool is the ass in Psalms
The fool in Sirach is the Ant
The fool is what you don’t want to be
The fool is what God tells you not to be
But he protects them
He understands them
He created them

If that is what I need in order to have his shield
I pray to be the fool
I pray to be protected
Maybe that is why ignorance is bliss at times
Maybe that is why they say that
Maybe a fool said that
And see how his words still last?
But maybe he didn’t last
Because with that statement
I think he lost his ignorance
Because he knew it was bliss
His ignorance, no longer folly, but purpose
And I don’t even know his name
But was that fool protected?
I hope he was
For my sake....
For our sake.

Marshall Fleurant, MD
WOMAN WITH RELAPSING FEVERS

Mary Kate McCullen, MD

Case Presentation
A 50 year-old Nigerian woman with a past medical history significant for type II diabetes and hypertension presented to the ED with a chief complaint of recurrent fevers and chills. The patient was in her usual state of health until approximately 6 weeks prior to admission, while during a visit with family in Nigeria she noted the onset of high fevers and general malaise. Initially, her fevers occurred daily for a period of one week, and were associated with chills, fatigue, loss of appetite, and myalgias. During this time, she was not evaluated by a physician, nor did she take any medication. Her symptoms seemed to resolve however, and she felt reasonably well. She then returned home to the United States, approximately 4 weeks prior to admission. Upon return, she again experienced one week of recurring fevers/chills, as well as the above generalized symptoms. With no evaluation or intervention, her symptoms improved. Two weeks later, the same pattern of symptoms returned and the patient reported to the ED.

Upon presentation, the patient complained of subjective high fevers, shaking chills, anorexia, fatigue, generalized weakness, myalgias, and 15 pound weight loss during the prior 6 weeks. She denied sick contacts and known TB exposures. She traveled with her son, who remained in his usual state of health. She reported that the areas to which she traveled were heavily mosquito-infested.

Her past medical history was significant for type II diabetes and hypertension. Her home medications included metformin 500 mg twice daily and diovan/HCTZ 160/25 once daily. There were no recent medication changes and she denied drug allergies. She had no history of alcohol, tobacco, or substance abuse. Her mother and father were both alive and well, living in Nigeria. She is employed as a chef, but had not been to work since before her visit to Nigeria.

Physical exam revealed a well-nourished woman in no apparent distress. Her temperature was 102.8; pulse 88 beats/minute; blood pressure 144/78 mm Hg; respiratory rate 16 breaths/minute; and pulse ox 100% on room air. Her sclera were anicteric and mucous membranes were dry. She had a normal S1S2, with a regular rate and rhythm, and no murmurs, rubs, or gallops. Her lungs were clear to auscultation bilaterally and she had no peripheral edema. Her abdomen was soft, non-tender, non-distended, with no hepatosplenomegaly. Her neurologic exam was non-focal; she was awake, alert, and oriented to person, place, and time.

Laboratory evaluation showed a normal complete blood count, chemistry panel, and liver function panel. A urinalysis revealed trace protein and trace ketones. Her EKG showed NSR with no ischemic changes. A blood smear was reviewed and revealed intra-erythrocytic ringforms consistent with Plasmodium (Figures 1 and 2). A diagnosis of malaria was made and the patient was immediately started on quinine and doxycycline. Despite oral therapy, the patient was admitted to the hospital to follow her fever curve and await speciation. The patient remained afebrile after ~ 36 hours of antibiotic therapy. The microbiology lab performed a Giemsa stain of thin and thick smears, revealing Plasmodium falciparum with a 20% parasitemia level. Her labs were followed in house as well, with no evidence of renal compromise or LFT abnormalities. She was discharged home to complete a 7 day course of quinine and doxycycline.
Discussion

Approximately 300 to 500 million cases of malaria occur annually worldwide, particularly in children living in tropical developing countries. Infection rates have increased in recent years, secondary to factors including increased resistance of parasites to drug therapy, increased resistance of the Anopheles mosquito to insecticides, climate changes, and increased travel to endemic regions. Globally, the areas of greatest transmission include Oceania and sub-Saharan Africa; other regions with high risk of transmission, in descending order, are the Indian subcontinent, Southeast Asia, South America, and Central America. Travelers from industrialized countries are at risk for malaria as well; approximately 30,000 of them contract the disease each year. Worldwide, an alarming 700,000 to 2.7 million deaths occur each year.

Malaria transmission occurs predominantly via a bite from the female Anopheles mosquito. There are other rare means of transmission, including congenital acquisition, blood transfusion, needle sharing, and organ transplant. In the United States, Anopheles mosquitoes are present in all states, except Hawaii. Although extremely rare, mosquito-borne transmission in the US has occurred. An outbreak of malaria was reported in West Palm Beach, Florida in 2003, with 7 documented cases of Plasmodium vivax infection.

There are four species of Plasmodia: P. falciparum, P. vivax, P. ovale, and P. malariae. Human infection by each of them occurs when sporozoites are transmitted from an infected anopheline mosquito during a bite. The sporozoites travel via the bloodstream to the liver, where they invade hepatocytes and divide thousands of times into mature tissue schizonts. Each schizont contains thousands of daughter merozoites. After 6-16 days, the liver schizonts rupture, releasing merozoites into the bloodstream where they invade red blood cells.

Within the RBCs, merozoites mature from ring forms to trophozoites to mature red cell schizonts (asexual); daughter merozoites are then released and able to infect new red cells. Some merozoites will differentiate into male and female gametocytes (sexual) which circulate in the bloodstream until they are ingested by a blood-feeding anopheline mosquito. Sporozoites then form in the mosquito and will eventually reinfect humans.

Mosquito-transmitted P. vivax and P. ovale infections carry a unique risk; some parasites remain dormant in the liver and may cause late relapse by reactivating after several months.

The pathogenesis of malaria is several-fold. All four species may cause anemia via alteration of red cell membranes resulting in hemolysis, accelerated splenic clearance, and digestion of red cell proteins and hemoglobin. Additionally, red cell lysis releases tumor necrosis factor alpha, which in turn suppresses hematopoiesis. Thrombocytopenia may result from increased splenic sequestration and decreased platelet survival time.

P. falciparum may cause especially severe or fatal disease via formation of “sticky knobs” on the surface of erythrocytes. These may bind to receptors on endothelial cells in capillaries and venules, leading to sequestration and subsequent obstruction to blood flow, which can result in secondary organ dysfunction.
Several genetic factors have been suggested as protective mechanisms against severe infection. For example, presence of the sickle cell trait has been shown to lower the risk of *P. falciparum* malaria, lower parasite densities, and lower rates of hospital admissions. Alpha and beta thalassemia have been shown to be associated with decreased rates of parasite multiplication, as well.

Individuals who live in endemic areas may develop partial immunity to disease after repeated infections; they become “semi-immune.” This does not completely prevent infection however; after a bite from an infected mosquito, they will develop parasitemia, but the severity of symptoms may be less. This partial immunity often wanes after leaving an endemic area. Therefore, when these individuals return home to endemic areas, they must take prophylaxis.

Malaria infections usually become symptomatic during the erythrocytic stage of the parasite life cycle; incubation periods for *P. falciparum* are usually 12 to 14 days, 2 months for *P. vivax* and *P. ovale*, and finally 35 days for *P. malariae*. The erythrocytic stage of infection usually lasts approximately one to four weeks. Malarial signs and symptoms may vary, but essentially all infected patients exhibit fever; it develops with the release of merozoites from rupture red blood cells. Fevers occur in paroxysms which are often daily and irregular. Other common symptoms may include chills, sweats, headache, myalgias, fatigue, nausea, vomiting, abdominal pain, diarrhea, and cough. Signs of infection may include anemia, thrombocytopenia, splenomegaly, hepatomegaly, and jaundice. Nephrotic syndrome occurs in some cases, and is most commonly associated with *P. malariae*.

*P. falciparum* in particular has been noted to have severe morbidity and mortality. Untreated *falciparum* infections can be fatal. This species has the ability to invade red cells of all ages, thereby allowing high levels of parasitemia, sometimes involving more than 50% of red cells. As noted above, *P. falciparum* is more likely to lead to secondary end organ damage than the other species because of its ability to adhere to blood vessels and create obstruction to flow. Cerebral malaria is one rare, but potentially fatal effect of the infection. It usually presents with an impaired state of consciousness or seizures, and may result in coma or death; 20% of treated adults and 15% of children may die. Other complications of *falciparum* include oliguric renal failure, pulmonary edema/ARDS, hypoglycemia, anemia, and gastroenteritis.

Conventionally, malaria has been diagnosed by light microscopy of a Giemsa-stained thick and/or thin blood smear; this is the gold standard. The thick smear is more sensitive in the diagnosis of malaria, however the thin smear facilitates exam of the parasite morphology which aids in species identification. The thin smear is also used to quantify the percentage of parasitized red cells. PCR-based techniques are also available; they detect nucleic acid sequences specific to Plasmodium species and are helpful when light microscopy is equivocal in species identification. The sensitivity and specificity of PCR approach 100 percent. Other antigen detection methods and serologic assays are available, but their sensitivity decreases with lower levels of parasitemia.

Most patients with *P. vivax*, *P. ovale*, and *P. malariae* can be treated as outpatients. Those with *P. falciparum* however, should be admitted to the hospital for initiation of their treatment and observation for any evidence of complications. None of the available anti-malarial drugs act on all stages of the malaria life cycle to kill the parasite; therefore, patients require multi-drug regimens. Choosing an appropriate regimen depends upon the species and pattern of drug resistance.

*P. ovale*, *P. malariae*, and chloroquine-sensitive *P. vivax* can be treated with oral chloroquine, with cure rates exceeding 95 percent. Patients with chloroquine-resistant *P. vivax* may be treated with a combination of mefloquine or quinine sulfate and doxycycline. In *P. vivax* and *P. ovale* infection, relapse after chloroquine therapy is common secondary to the presence of liver hypnozoites lying dormant. Therefore, primaquine should be given to all of these patients for fourteen days, immediately after finishing their course of chloroquine. All patients must be screened for G6PD deficiency before starting primaquine therapy to avoid hemolysis.

Chloroquine-resistant *falciparum* is now widespread throughout most countries; therefore, *falciparum* infections should be presumed to be chloroquine-resistant in almost all cases. The most commonly recommended regimen for this is oral quinine plus pyrimethamine-sulfadoxine or doxycycline for seven days. An alternative is quinine plus clindamycin, particularly for pregnant women or young children. Quinine-based regimens have greater than 90 percent efficacy in most parts of the world, except Southeast Asia where resistance is prevalent. There are alternative regimens as well, including mefloquine, atovaquone-proguanil, and artemisinin derivatives.

It is essential to stress the importance of taking chemoprophylaxis when patients travel to endemic areas. Most cases of malaria in the US are in patients who have not taken prophylaxis or those who have stopped taking it too soon after return home. Chloroquine should be used for areas where there is no chloroquine-resistant *P. falciparum*; it should be started 1-2 weeks before the patient departs and continued for 4-6 weeks after leaving the endemic area. Travelers to chloroquine-resistant areas should take mefloquine for prophylaxis. After travel to areas with *P. vivax* and *P. ovale*, patients should take primaquine during the last two weeks of a prophylaxis period.

**References**

AN UNUSUAL LOCATION FOR PROSTATE BRACHYTHERAPY SEEDS
Sivakumar Srinivasan, MD, and Sandeep Anreddy, MD

Introduction
Vascular migration of radioactive seeds to the lungs after prostate brachytherapy is known phenomenon. Here in we report a case of prostate brachytherapy seed migration into the right ventricle.

Case Presentation
An 83 year-old male with a past medical history significant for hypertension, hyperlipidemia, and prostate cancer status post prostate brachytherapy seed implantation was brought to the Cardiac catheterization lab for an elective catheterization for further evaluation of a recent stress test revealing antero-apical ischemia with an ejection fraction of 49%. The Cardiac catheterization films are shown below (Figures 1 and 2).

Discussion
Prostate brachytherapy is achieved with radioactive seed implantation carrying iodine-125 or palladium-103. This procedure is a well-accepted therapeutic option for patients with localized prostate cancer. The small size of the seed allows for potential displacement from the periprostatic insertion site to adjacent prominent periglandular venous plexuses. The most common site of prostatic seed migration is the pulmonary vasculature barring a congenital arterio-venous malformation or congenital heart disease.

Prior reports indicate that the percentage of patients who have at least 1 seed migrate to the chest following prostate brachytherapy varies widely from 0.7% to 55%, whereas the total percentage of seeds that eventually migrate is less than 1%. Seed embolization to the heart is extremely rare. The true incidence rate has not been reported. Seed migration to the heart can rarely cause cardiac arrhythmias. A chest X-ray is commonly recommended following brachytherapy and during routine follow-up evaluation.

References
**ACUTE MYOCARDIAL INFARCTION AFTER BLUNT CHEST TRAUMA**

*Sivakumar Srinivasan, MD, Sandeep Anreddy, MD, and Paul Mather, MD*

**Introduction**

Coronary artery injury rarely occurs after blunt chest wall trauma. It can, however, lead to extensive myocardial infarction. We report a rare case of acute anterolateral myocardial infarction in a young man after blunt chest trauma.

**Case Presentation**

A 30 year-old man was transferred to the emergency room after a motor vehicle accident. He was an unrestrained passenger in an ambulance and was ejected from the vehicle on impact resulting in multiple injuries including blunt chest trauma. Upon arrival to the emergency room his blood pressure was 118/69 mmHg and pulse rate 95/min. Initial physical examination revealed multiple large abrasions across bilateral anterior chest wall and normal cardiovascular, respiratory and abdominal examinations. Routine EKG showed Q wave and ST segment elevation throughout the precordial leads as well as leads I and aVL (Figure 1).

The initial laboratory results including chemistry panels and blood counts were normal, however cardiac specific troponin was 152.40 ng/mL. Urgent two-dimensional echocardiography showed apical, septal, and anterior wall akinesis with resultant severely depressed left ventricular function.

A diagnostic coronary angiogram revealed 100% occlusion of the proximal LAD distal to the origin of the first septal perforator. The lesion was associated with a moderate filling defect consistent with thrombus. Percutaneous coronary intervention was successfully performed for the lesion and the post-procedural angiogram showed excellent coronary flow without residual stenosis (Figures 2 and 3). Follow up cardiac specific troponin I on day 9 was 2.90 ng/mL.

**Discussion**

This case presents a rare complication of blunt chest trauma. To save myocardium from ischemic injury, prompt diagnosis is vital and routine EKG check should be performed in all the patients with chest trauma. Observations from case series suggest that the mechanism leading to myocardial infarction after blunt chest trauma is a shear force applied to the coronary artery with resultant intimal tearing. This injury precipitates platelet aggregation and intracoronary thrombosis. The higher incidence of left anterior descending artery involvement may be due to the proximity of this artery to the chest wall. Most trauma patients will not be candidates for thrombolytic therapy because of the high risk of bleeding from concomitant injuries. Given a skilled catheterization laboratory team, direct PTCA can be performed in seriously ill patients quickly and with outstanding results without the necessitate for thrombolytic agents.

**References**

WOMAN WITH ANEMIA AND ABDOMINAL PAIN
Joanna Kipnes, MD, and Marina Serper MD

Case Presentation
The patient is a 36 year-old African American female with a 15 year history of Crohn's disease complicated by severe perianal involvement not responsive to steroids or immunomodulating medication. The patient had undergone a proctocolectomy and diverting ileostomy two years ago secondary to refractory disease and had been symptom-free until 6 months prior to admission. At that time, the patient noted pain, vaginal discharge, and ulcerations in the perineal region. Three weeks prior to admission, she began to have almost daily vaginal bleeding as well as weakness, dizziness, and increased fatigue. She had no subjective fevers or chills and had no changes in output from the ileostomy. Outpatient medications included ciprofloxacin and metronidazole started 3 days ago by her gastroenterologist.

On physical examination, the patient was a well-nourished female in no apparent distress. Her blood pressure was 126/72 mmHg, the pulse was 80 beats per minute, the temperature was 98.6° F and the oxygen saturation was 100% on room air. She was anicteric with moist mucous membranes and normal skin turgor. On cardiac examination there was a 1/6 systolic ejection murmur heard best at the left sternal border. The lungs were clear to auscultation. The abdomen was soft, diffusely tender, with the ileostomy draining odorless bilious material. She had normal bowel sounds. No lower extremity edema and no rashes were present.

Gynecologic examination revealed left labial swelling, and two ulcerations, 1 to 2 cm in size, between the labia major and minora. There was another linear midline ulceration extending from the gluteal cleft to the perineum. At that time, an internal examination could not be performed secondary to severe pain.

Admission labs were notable for hemoglobin of 5.9 g/dL, MCV of 60 fl, CRP of 2.3 mg/L, and ESR of 63 mm/hr. A CT scan of the abdomen and pelvis showed marked distension of the vaginal lumen and vaginal stenosis likely secondary to inflammation.

The patient's profound iron deficiency was treated with a blood transfusion and IV iron. A differential diagnosis for the perineal lesions included enterovaginal fistulae, cutaneous Crohn's disease, Bechet's disease, and sexually transmitted diseases.

A vaginal exam conducted under anesthesia revealed extensive linear vulvar ulcerations extending from the perineum to the gluteal cleft. During the examination a copious amount of green malodorous fluid was extracted from the vaginal vault. No fluctuant masses, internal vaginal lesions, or fistulous tracts were identified. A pelvis MRI showed a vaginocutaneous fistula, but no communication between the vagina and the GI tract. A small bowel follow-through showed a normal mucosal pattern and no enterovaginal fistula. The patient also had a negative charcoal challenge test in which a tampon was placed in her vagina and the patient drank activated charcoal. No charcoal was identified on the tampon (a negative test) indicating that no enterovaginal fistula was present.

Vulvar biopsy (Figure 1) showed dense diffuse inflammation with multinucleated giant cells and granulomas consistent with Crohn's disease. Further workup for infectious etiologies (HSV, syphilis, H. ducreyi, Chlamydia, Gonorrhea) was negative. The presence of histology consistent with Crohn's disease and the absence of an enterovaginal fistula established the diagnosis of cutaneous Crohn's disease also known in the literature as metastatic Crohn's disease.

Discussion
Crohn's disease is a chronic, relapsing disease that may affect any part of the alimentary tract from the mouth to the anus. Skin lesions are well recognized as an extra intestinal manifestation of Crohn's disease. Cutaneous lesions may be divided on the basis of whether or not they have a granulomatous histologic appearance. Lesions without a granulomatous appearance are more common and include erythema nodosum, pyoderma gangrenosum, Sweet syndrome, and epidermolysis bullosa acquisita.

Granulomatous cutaneous lesions of Crohn's disease most commonly affect the skin through direct contiguous extension from the involved bowel. However lesions that form noncaseating granulomas in sites noncontiguous with the gastrointestinal tract have been termed “metastatic Crohn's disease.” The lesions of metastatic Crohn's disease were first described by Parks et al. in 1965 and have since been reported involving the face, axilla, pulmonary mucosa, vulva, vagina, penis, scrotum, forearms, shins, breast, back, perianal region, and groin. The lesions may appear as ulcers, nodules, ulcers, or plaques. Because of its variable appearance it has been misdiagnosed as cellulitis, erysipelas, lichenoid eruptions, or various sexually transmitted diseases.

Metastatic Crohn's disease has been reported in the absence of any active gastrointestinal disease, however it more commonly occurs in those with colonic involvement and does not parallel...
The patient is a 67 year-old male with past medical history of CAD s/p CABG, CHF with EF of 15%, BiV- ICD, who was recently admitted to an outside hospital in Delaware with SOB and weakness, and was found to have frequent bouts of VT. During that hospitalization, he had suffered cardiac arrest as well, and epinephrine was administered emergently through a peripheral IV site located in his right hand. He was thereafter loaded with amiodarone for the ventricular tachycardia. It was later found that the epinephrine had infiltrated into the skin of his right hand from the peripheral IV site. Following stabilization at the outside hospital, the patient requested transfer to Wilmington VAMC for further treatment and rehabilitation. The photograph below (obtained with permission), illustrates the vast degree of skin necrosis and surrounding erythema that resulted from skin infiltration of epinephrine in this patient.

Vasoactive drugs are often administered immediately before, during, and after an arrest to support cardiac output. Drugs may be selected to improve chronotropy, inotropy, or arterial pressure. The emergent nature of a cardiac arrest code often demands expedient administration of IV medications, at times through a peripheral IV site. This is done, however, with a certain amount of risk. In the event that extravasation develops, immediately infiltrate 5 to 10 mg of phentolamine diluted in 10 to 15 mL of saline into the site of extravasation to prevent tissue necrosis, such as that observed in the above photograph.

References
Case Presentation
The patient is a 69 year-old male with new onset jaundice of two weeks and a 6 month history of progressive hyperbilirubinemia with cholestasis who was admitted for evaluation. Physical examination revealed a well developed and well nourished, jaundiced male with scleral icterus, a II/VI systolic murmur at apex, mild abdominal discomfort over epigastrum on palpation without discernable hepatomegaly, normal distal pulses, no lower extremity edema, and no stigmata of chronic liver disease. Laboratory investigation revealed a total bilirubin of 19.3 mg/dL, alkaline phosphatase 693 U/L, and AST and ALT of 140 U/L and 117 U/L, respectively. CT scan of the abdomen and pelvis showed multiple foci of arterial enhancement, periportal edema without biliary dilatation, concerning for acute fulminant hepatitis. The patient had a dramatic and rapid decline the day following admission, developing cardiac arrhythmia and hypotension and subsequently died despite resuscitative efforts. Autopsy revealed amyloidosis AL, kappa light chain type involving the liver (Figures 1 and 2), heart (Figures 3 and 4), lungs and bone.

Discussion
Although hepatic involvement is a common manifestation of primary amyloidosis, systemic amyloid presenting with jaundice and severe cholestasis is rare and portends a poor prognosis. Amyloidosis manifesting as cholestatic liver disease has the shortest mean survival of any presentation of the disorder, approximately 3 months from the identification of jaundice; only 25% of patients live longer than 6 months. While the most common cause of death in amyloid is due to congestive cardiomyopathy or sudden death due to VF or asystole, the presence of heart failure suggests a six month clinical predictor of survival. Patients with AL often suffer from rapid-onset heart failure.
Case Presentation
A 28 year-old Caucasian female, 3.5 months postpartum, presented to the TJUH ED with facial and neck swelling. She was in her usual state of health until approximately 1 month prior to admission when she noted the gradual onset of neck swelling. The neck swelling progressed to her face 4 days prior to admission; swelling in both areas was progressive and increasingly uncomfortable. Two months prior, the patient was treated for sinusitis with a course of antibiotics by an allergist; this treatment was unsuccessful, and she was referred her to an otolaryngologist, who performed a neck ultrasound and lab work. The patient reported that several enlarged lymph nodes were found in her neck. The patient was then sent for a CT of the neck and chest, which showed a mass in her mediastinum. She was planning to follow up with a cardiothoracic surgeon, however she developed symptomatic swelling and intermittent dysphagia. The patient described a sensation of choking and strangulation; these sensations came and went at random times. She also reported tolerating only small amounts of soft foods, such as apple sauce, Jell-O, and yogurt. The dysphagia was present only with solid foods, not with liquids.

The patient also complained of dull upper back pain located in her upper right trapezius area for the past month which was exacerbated by holding her child and other physical activities and was alleviated somewhat by ibuprofen; this pain felt like a pulled muscle and she rated it 4/10. She stated that chest pain, located at her right anterior chest, had bothered her for the last 4 days; she described this pain as piercing, sharp, 9/10 in severity, and intermittent, with no exacerbating or ameliorating factors.

The patient’s past medical history included intermittent migraines for several years which were well-controlled and a full term...
uncomplicated vaginal delivery four months prior after which she breast fed for 6.5 weeks. Her surgical history was significant only for appendectomy and breast augmentation. She was taking no medications and reported allergies to penicillin, latex, iodine, and shellfish, which all cause pruritic rash. She denied alcohol, tobacco, or substance abuse. Her family history was noncontributory.

Her review of systems was significant for 7 lb weight gain in the last week, congested and swollen right ear, bilateral sinus pressure, hoarseness, bulging veins which appeared in left neck 1 week ago, and occasional pulsations in her neck bilaterally. She reported edema in the right hand, bilateral swelling of hands and fingers (right greater than left, worsening recently), as well as tingling and numbness in the right fingertips. The patient reported feeling light-headed when sitting up from supine or when bending over to pick something up off floor, and she felt that her neck swelling worsened when leaning forward. The patient also reported intermittent throbbing headaches, minimally relieved by ibuprofen.

On physical exam, the patient was in no acute distress with stable vital signs. The head and neck exam was significant for an enlarged, well-developed neck with visible tortuous collateral vessels bulging on the left side. Neck circumference was 31.5 cm. Sternocleidomastoids were prominent bilaterally. There was no cervical or supraclavicular lymphadenopathy, nodules, or enlarged thyroid. The patient had maxillary and frontal sinus tenderness to palpation bilaterally, right greater than left. No stridor was appreciated. Generalized distension in neck prevented clear assessment of jugular venous pressure. Pemberton sign was negative. Examination of the lungs revealed decreased breath sounds on right side. Extremity exam revealed dusky/dark appearance of the skin of right extremities and edema of right hand. No axillary or inguinal lymphadenopathy present.

Assessment

The constellation of this patient’s history, signs and symptoms, labs, imaging studies, and knowledge of presence of mediastinal mass were consistent with Superior Vena Cava (SVC) Syndrome. This diagnosis was supported by known presence of anterior superior mediastinal mass with SVC displacement, swelling of the neck and face, development of collateral neck vessels, unilateral cyanosis, swelling and tingling and numbness of the upper extremity, and positional lightheadedness.

Hospital course

Initial serologic studies were unrevealing. Chest x-ray in the ED revealed a widened superior mediastinum. CT of the chest performed shortly prior to presentation forwarded from an outside institution showed a large homogeneously enhancing anterior mediastinal soft tissue mass insinuating between aortic branch vessels, displacing the SVC laterally with compression. The mass was measured at 9.4cm x 4.9cm x 13.8cm. The patient underwent bronchoscopy and transbronchial biopsy of the mediastinal mass, but pathology was indeterminate. Cardiothoracic surgery was consulted for mediastinoscopy, and biopsies revealed Hodgkin’s lymphoma, nodular sclerosing subtype (see Figures 1-4). Both Medical Oncology and Radiation Oncology were consulted, and treatment plan was made. The patient underwent bilateral bone marrow biopsies which were negative. Remainder of the staging work-up was significant only for enlarged lymph nodes in the prevascular and pretracheal spaces. The patient’s disease was staged at IIA.

Discussion

Superior Vena Cava syndrome (SVCS) occurs when the SVC is invaded or externally compressed by a mass or thrombosed. SVCS encompasses a classic constellation of signs and symptoms including facial edema, dyspnea, tachypnea, cyanosis, venous distension, headache, and plethora. Other signs include cough, arm edema, a feeling of head fullness often exacerbated by lying down or bending forward; more seriously, it could present as respiratory distress from tracheal involvement. Pemberton’s sign is the development of facial plethora, inspiratory stridor, and non-pulsatile JVP elevation when a patient with SVC syndrome lifts the arms over the head. While dysphagia, hoarseness, and stridor are not included in the definition of SVCS because they result from compression of mediastinal structures other than the SVC (esophagus, laryngeal nerve, and trachea respectively), their presence is negatively correlated with prognosis. Presentation depends on both the location and rate of growth of the mass; growth rate also determines how well the syndrome can be compensated by new collateral circulation. Important collateral veins arise from the azygos, lateral thoracic, paraspinal, and internal mammary veins. Approximately 85% of cases of SVCS are caused by malignant tumors; the rest are due to infection and thrombosis. Up to 60% of patients presenting with SVCS due to underlying malignancy present without a known diagnosis of cancer. The most common malignant causes of SVCS are lung cancer, lymphoma, thymoma, mediastinal germ cell tumors, and solid organ tumors metastatic to the mediastinum. Bronchogenic carcinoma and lymphoma alone account for 94% of cases of SVC syndrome. Fibrosing mediastinitis accounts for up to 50% of nonmalignant causes of SVCS. This clinical entity is often caused by excessive host cell response to a prior Histoplasma capsulatum infection; however, other causative infections include aspergillosis, blastomycosis, actinomycosis, tuberculosis, and Bancroftian filariasis. SVC thrombosis can also occur secondary to indwelling central venous catheters and pacemaker leads.

Lung carcinoma is the most common cause of SVCS and does so via compression or direct SVC invasion by tumor or via mediastinal lymphadenopathy. Two to four percent of patients with lung carcinoma develop SVCS during the course of their disease. Up to 20% of patients with small cell lung cancer develop SVCS because of the central location of these tumors; peripherally arising lung tumors, including adenocarcinoma and large cell carcinoma, are less likely to cause SVC involvement. Small cell...
lung cancer accounts for approximately 40% of all cases of SVC syndrome due to lung cancer, with squamous cell carcinoma making up another 18%.

Lymphoma, almost always Non-Hodgkin's type, is the second most common cause of SVCS. Approximately 2-4% of patients with lymphoma develop SVCS, via lymph node enlargement. The most common lymphomas associated with SVCS are diffuse large B-cell and lymphoblastic lymphomas. Hodgkin's lymphoma, despite its common presentation with mediastinal lymphadenopathy, rarely causes SVCS.

In addition to lung carcinoma and lymphoma, thymoma and germ cell tumors are also among the more common malignant causes of SVC syndrome.

Anterior Mediastinal Masses
Approximately 2/3 of all mediastinal tumors are benign. Anterior mediastinal masses make up 60% of all mediastinal masses. The most common neoplasias of the anterior mediastinum include the “4 Ts” – thymoma, thyroid tumor, germ cell tumors (teratomas), and “terrible” lymphomas. Other anterior mediastinal neoplasms include thymic carcinoid, thymolipoma, and parathyroid adenomas. Thymic cyst, lymphangioma, and intrathoracic goiter comprise the non-neoplastic causes of anterior mediastinal masses.

Lymphoma is the second most common primary anterior mediastinal tumor, second only to thymoma, and accounts for 10-20% of primary mediastinal masses overall. While lymphoma can affect any mediastinal compartment, most are located in the anterosuperior mediastinum and the remainder in the middle mediastinum. These lymphomas typically present with large, bulky tumors, often with involvement of adjacent intrathoracic structures. While Hodgkin's lymphoma represents only 25-30% of all cases of lymphomas, it is the most common mediastinal lymphoma; the nodular sclerosing subtype is the most common, and it has particular predilection for the anterior mediastinum. Hodgkin's lymphoma will be discussed below. The most common primary mediastinal Non-Hodgkin's lymphomas are large B-cell lymphoma and lymphoblastic lymphoma. Patients with NHLs are typically older than age 55; 85% present with advanced disease and typically have constitutional (“B”) symptoms, generalized lymphadenopathy, and extensive extranodal disease at time of diagnosis. Indolent NHLs, as compared to aggressive NHLs, generally have a more favorable histologic condition, occur nodally, and are more clinically advanced at presentation. Treatment of NHL depends on histologic classification, site of presentation, and disease extent. Patients with indolent NHLs are treated palliatively with radiation and chemotherapy if necessary, as they typically have a more prolonged disease course, are rarely cured, and almost always have recurrence. Patients with aggressive NHLs are treated with combination chemotherapy and radiation, with possible bone marrow transplantation. Negative prognostic factors for NHLs include extensive extranodal disease and large tumor size at presentation, and slow response to treatment.

**Hodgkin's Lymphoma: Diagnosis, Staging, and Treatment**
Hodgkin's lymphoma, first described by Sir Thomas Hodgkin in 1832, is a malignant lymphoma with a bimodal peak incidence in the second and fifth decades, more commonly found in males. Diagnosis of Hodgkin's lymphoma requires presence of the classic Reed-Sternberg cell – with its abundant basophilic cytoplasm and two large nuclei with pale chromatin and distinct eosinophilic nucleoli – in a mixed inflammatory background of reactive lymphocytes, macrophages, plasma cells, eosinophils, and a disrupted nodal architecture with fibrotic stroma. Only recently were Reed-Sternberg cells discovered to be of B-cell origin; though these cells lack B-cell markers such as CD20 and the B-cell receptor, their precursors are definitively germinal center B-cells that escape negative selection and apoptosis by acquisition of a survival advantage through an as yet unknown mechanism. Epstein-Barr Virus is thought to play a role in the malignant transformation of Reed-Sternberg precursor cells by upregulation of antiapoptotic genes and inhibition of the FAS-signalling pathway.

The two main types of HL are classic HL and lymphocyte-predominant HL; classic HL is further classified into 4 subtypes, including nodular sclerosis, lymphocyte rich, lymphocyte depleted, and mixed cellularity. Classic HL accounts for 95% of all cases of HL. This discussion will center around the nodular sclerosing subtype as it is the most common, accounting for nearly 80% of cases of HL. With a predominance in young, female patients, the nodular sclerosing subtype is characterized by a nodular growth pattern with sclerosing/fibrotic collagenous banding. The pathology report for the patient in the above case stated that “the lymph node architecture appeared effaced by bands of collagen fibrosis, which subdivide the lymph node into smaller nodules.” Nodular sclerosing Hodgkin's lymphoma has a unique predilection for the anterior mediastinum, especially the thymus, and may manifest itself as a discrete, lobulated anterior superior mediastinal mass.

The most common clinical presentation of HL is enlarged nontender cervical and/or supraclavicular lymphadenopathy, and bulky mediastinal lymphadenopathy is additionally characteristic of nodular sclerosing HL. Patients with mediastinal involvement tend to be younger than those without mediastinal disease; mediastinal involvement can manifest as chest pain, cough, wheezing, dysphagia, or SVC syndrome, discussed above. At presentation, 25% of patients with HL have constitutional “B” symptoms of fever (including cyclic Pel-Ebstein curves), weight loss and night sweats. There is also an unusual association between alcohol consumption and lymph node pain or generalized pruritis in patients with Hodgkin's lymphoma.
Anatomic staging helps distinguish patients that would likely benefit from radiation therapy alone from those requiring systemic treatment. Most patients with HL present with disease localized above the diaphragm; approximately 50% of patients present in stage I or II, and less than 5-10% have extranodal disease at time of diagnosis. Subtype and stage are the two most important prognostic factors in HL: the nodular sclerosis subtype carries a very good prognosis, while lymphocyte-depleted HL carries the worst prognosis of the HL subtypes. Constitutional symptoms, age greater than 45, extranodal or bulky mediastinal disease, high ESR or LDH, and greater than five splenic disease foci are adverse prognostic factors.

Patients with stage IA, IB, IIA, and IIB disease are treated with combined-modality therapy of combination chemotherapy plus involved-field irradiation. This concept has replaced prior treatment plans of radiation therapy alone, which was associated with a high incidence of complications including gonadal toxicity and secondary malignancies. Combined-modality therapy also provides improved disease control and lower morbidity. Patients with stage III or IV disease receive combination chemotherapy in occasional combination with radiation.

The chemotherapeutic regimen of choice for Hodgkin's lymphoma is ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine. The MOPP regimen (mechlorethamine, vincristine, procarbazine, prednisone) was the first drug regimen that produced a high proportion of complete remissions in Hodgkin's lymphoma; ABVD was later introduced as a potentially curative salvage regimen and was shown in 1992 to be superior to the MOPP regimen as it is more efficacious and does not cause sterility. A 2003 trial comparing ABVD to a hybrid MOPP/ABV regimen showed that the hybrid regimen caused more life-threatening side effects during the initial treatment phase and had increased incidence of late complications of sterility and secondary malignancies, especially myelodysplastic syndrome and secondary acute leukemia, without any gain of efficacy. Four cycles of ABVD are used in early-stage disease and six to eight are used in advanced-stage disease. Relapsed disseminated disease is treated with high-dose chemotherapy and autologous bone marrow transplantation.

**Follow-up**

The patient described in the above case can expect a 12-year freedom from progression of approximately 94% and an overall survival rate of 94%.

**References**


Special thanks to Dr. William Kocher of the Department of Pathology for providing images and guidance.
WOMAN WITH FATIGUE, SHORTNESS OF BREATH, AND CHEST PAIN

Neilanjan Nandi MD, Sitakumar Srinivasan MD

Case Presentation
A 62 year-old African American female with past medical history significant for scleroderma, Raynaud’s phenomenon, and hypertension presented to the ED with 6 weeks of worsening fatigue, shortness of breath and a new onset of left sided chest pressure. Her outpatient medications included metoprolol 50 mg every 12 hours and nifedipine XR 90 mg once daily. On physical examination, the patient was noted to have a blood pressure of 189/62 mmHg and a pulse of 44 beats per minute. Her laboratory data including chemistry panel, complete blood count, and cardiac enzymes were unremarkable.

EKG was performed and the results are shown (Figures 1 and 2).

Discussion
In the spectrum of bradyarrhythmias, complete heart block represents a potentially life threatening condition frequently resulting in hemodynamic instability and death. Also known as third degree atrioventricular block (3º AVB), this lethal arrhythmia is caused by a complete disconnect between the sinoatrial (SA) and atrioventricular (AV) nodes manifesting in independent atrial and ventricular rhythms. This dissociation is caused by a conduction system block at the level of the AV node, the Bundle of His, or the Purkinje bundle-branch system. Many etiologies resulting in hemodynamic instability and death. Also known as third degree atrioventricular block (3º AVB), this lethal arrhythmia is caused by a complete disconnect between the sinoatrial (SA) and atrioventricular (AV) nodes manifesting in independent atrial and ventricular rhythms. This dissociation is caused by a conduction system block at the level of the AV node, the Bundle of His, or the Purkinje bundle-branch system. Many etiologies

Approximately 50% of AV block may be caused by conduction system fibrosis and sclerosis, otherwise known as idiopathic progressive cardiac conduction disease. Another 40% will be caused by either acute or chronic ischemic heart disease resulting in temporary, progressive, or permanent conduction system block.

Table 1. Causes of Complete Heart Block

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Cause</th>
</tr>
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<tbody>
<tr>
<td>50%</td>
<td>Idiopathic Progressive Cardiac Conduction Disease</td>
</tr>
<tr>
<td></td>
<td>Lenegre's Disease – Slow progression to 3º AVB</td>
</tr>
<tr>
<td></td>
<td>Lev's Disease – Sclerosis &amp; calcification of left sided cardiac tissues</td>
</tr>
<tr>
<td>40%</td>
<td>Ischemic Heart Disease</td>
</tr>
<tr>
<td></td>
<td>Acute MI – 20% develop AVB (8% w/1º AVB, 5% w/2º AVB, 6% w/3º AVB)</td>
</tr>
<tr>
<td>10%</td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td>Increased Vagal Tone</td>
</tr>
<tr>
<td></td>
<td>Valvular/Structural Disease – Aortic or Mitral valve disease, HOCM</td>
</tr>
<tr>
<td></td>
<td>Developmental/Genetic – Congenital, Familial</td>
</tr>
<tr>
<td></td>
<td>Infiltrative – Restrictive Processes, Malignancy</td>
</tr>
<tr>
<td></td>
<td>Connective Tissue Disease – SLE, Scleroderma,</td>
</tr>
<tr>
<td></td>
<td>Infectious – Bacterial Endocarditis, Lyme Disease, Syphilis, Chagas, Viral</td>
</tr>
<tr>
<td></td>
<td>Metabolic/Endocrine – Hyperthyroid, Myxedema,</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia, Hypokalemia</td>
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<td></td>
<td>Iatrogenic</td>
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effects of atropine will result in a relative vagolysis with subsequent unopposed sympathetic stimulation which only serves to increase the myocardial refractory period. This can dangerously exacerbate the complete heart block and further decrease the ventricular depolarizations and contractions leading to further hypotension and accelerate time to death.

Conclusion

The patient had a transvenous pacer placed emergently. After waiting a sufficient amount of time to rule out excess beta-blockade and calcium channel blockade, her heart block persisted and was attributed to progression of her scleroderma. A permanent pacemaker was promptly placed. Many etiologies exist to promote complete heart block. Autoimmune rheumatic diseases are no exception and may manifest as rhythm and conduction system disturbances resulting in sudden cardiac death. Electrocardiographic disturbances in autoimmune rheumatic diseases such as scleroderma are not insignificant and should be considered in the differential of complete heart block.

References


Poem

When It Rains

You ever stand in the rain,
Especially on a hot summers day,
And feel the rain drops drip from the top of your head,
Straight down till it soaks into the seams of your socks,
Do you remember pressing your foot down into your soggy shoe,
And feel bubbles flow between your toes,
And you just couldn’t resist that puddle,
That giant, deep, dark brown, muddy puddle,
You just had to raise your knee high....
Then stomp down on that puddle with a force equal to that of Thor’s lightning bolt,
You just had to do it,
Just had to,
You just couldn’t waste a good puddle,
You just couldn’t stay indoors,
Had too...just had to play in the rain...
My mother used to tell me the rain was God’s tears,

The rain cooled you,
It played with you, watered you,
It surrounded you...fully,
It fed the trees, and filled the oceans,
You knew you were going to get wet...
You knew you were going to get sick...
You knew your mom was going to yell at you...
And that you were going to track muddy stains all over the floor...
You’re going to get punished...
And it served you right.
You ruined your clothes,
Got yourself sick,
Messied up your hair,
Dirtied the house,
And you rejoiced in God’s tears.
And you also knew......
That you couldn’t wait till the next rain shower.

Marshall Fleurant, MD
MAN FEELING TIRED AND “LOUSY” FIVE DAYS FOLLOWING MYOCARDIAL INFARCTION

Andra Popescu, MD

Case Presentation
A 70 year-old male presents to his cardiologist’s office with complaints of feeling fatigued and “lousy”. His past medical history is significant for HTN and HL, but until a recent hospitalization, he was non-compliant with his outpatient medical regimen. Of note, he also has a history of heavy alcohol consumption and a 30 pack-year smoking history. The patient reports that he was recently discharged after acute myocardial infarction (AMI) from an outside hospital. At that time, he underwent a diagnostic cardiac catheterization, but no intervention was performed secondary to 100% RCA stenosis and technical difficulties. He was sent home on clopidogrel, aspirin, metoprolol, lisinopril and simvastatin. He currently appears tired and anxious, however he has no symptoms of chest pain, dyspnea, orthopnea, diaphoresis, or lightheadedness; he does report that his primary symptoms leading him to admission was chest pain and shortness of breath.

On physical exam, the patient’s blood pressure is 75/56 mmHg with a heart rate of 89 beats per minute, respiratory rate is 18, and his room air oxygen saturation is 98%. Cardiac exam revealed a new apical systolic murmur best heard at the posterior axillary line radiating towards the scapula with an S3 present. JVP was estimated to be 20 cm H2O. Lung exam demonstrated bibasilar crackles. Peripheral extremities were warm with no lower extremity edema.

Initial laboratory data include a creatinine of 2.7 mg/dL (baseline 1.3 mg/dL), hemoglobin of 11.8 g/dL, a white blood cell count of 12,500 cells/mm3 without left shift or band forms, and troponin of 5.89 ng/mL. EKG revealed a normal sinus rhythm with ST elevations in leads II, III, aVF and ST depressions throughout the lateral precordial leads suggesting ongoing inferolateral ischemia or injury.

The patient was admitted to the Cardiac Care Unit (CCU) for further medical management. He received fluid boluses for BP support. Aspirin and statin therapy were continued and additionally, therapeutic intravenous heparin was initiated. Clopidogrel was held due to a potential need for surgical intervention. Beta blocker and ACE inhibitor were discontinued secondary to hypotension.

Cardiac catheterization reports were obtained from the outside hospital and demonstrated a 100% RCA stenosis. Additionally, there was diffuse disease throughout the coronary arteries including a 50% LAD, 50% LCx, 50% OM1, and 60% D2 stenosis with an ejection fraction of 35%. An echocardiogram obtained upon admission to this institution visualized a mobile echodensity attached to the chordal region of the anterior mitral leaflet suggestive of partial papillary muscle rupture leading to anterior leaflet prolapse, as well as systolic dysfunction due to multiple segmental wall motion abnormalities. Doppler evaluation confirmed severe, posterirolaterally directed mitral regurgitation with a “shoulder” sign, suggestive of severe, acute MR likely secondary to papillary muscle rupture.

Due to the patient’s acute renal failure, RCA angioplasty was not performed despite persistent ST elevations suggestive of ongoing ischemia. Right heart catheterization was performed which demonstrated a RA pressure of 10 mmHg, RV pressure of 43/15 mmHg, PA pressure of 42/23 mmHg, and a pulmonary capillary wedge pressure of 21 mmHg without significant v-wave. Cardiac index was measured at 1.5 L/min/m2, consistent with cardiogenic shock. Intra-aortic balloon counterpulsation was not performed due to the presence of severe PVD. The patient was started on a dopamine drip and taken to the operating room for emergent coronary bypass revascularization and mitral valve replacement.

The post-operative course was complicated by cardiac arrest and ventricular fibrillation. A trans-esophageal echocardiogram following resuscitation revealed a new 2 mm inferoseptal VSD. Multi-system organ failure ensued and the patient expired 9 days following bypass surgery.

Discussion
This is an excellent example for a discussion of mechanical complications following myocardial infarction. Our patient had two of the three major complications: rupture of the free wall, rupture of the ventricular septum and mitral regurgitation, each of which can result in cardiogenic shock.

1. Rupture of the ventricular free wall is a very serious and often lethal complication which usually occurs within the first 5 days post MI and has an incidence of less than 1% when all AMI patients are considered,1 but its incidence is between 14-26% among patients dying of acute MI.2,3 Risk factors for free wall rupture were large ischemia territory, lack of collateral blood flow (no history of previous angina or MI),3 anterior MI, age> 70, and female sex.4,5 Rupture typically occurs in an area that has been infarcted without successful reperfusion.6 There was an increased occurrence noted in patients treated with thrombolytic therapy versus patients who underwent coronary intervention (3.3% vs. 1.8%).7 Complete rupture of the left ventricular free wall is suggested by the development of sudden right heart failure and shock due to hemopericardium with resultant electromechanical dissociation. Incomplete, or subacute, rupture occurs when organized thrombus and pericardium seal the perforation forming a pseudoaneurysm. Management is with fluids resuscitation, ionotropic and/or vasopressor support, pericardiocentesis, IABP counterpulsation, and percutaneous cardiopulmonary bypass. Surgical repair is indicated for pseudoaneurysm. Prognosis is very poor and mortality is exceptionally high.
2. Rupture of the interventricular septum typically occurs 3-5 days after an acute MI, however, it may develop within the first 24 hours or as late as two weeks. Risk factors include “wrap around” LAD covering a large myocardial territory, extensive myocardial damage, poor septal collateral circulation, or RV infarction. Incidence has decreased from 2% in the conventional therapy era to 0.2% in the reperfusion therapy era. Although not a predisposing factor for septal rupture, thrombolysis may precipitate the occurrence. Rupture develops at the margin of the necrotic and non-necrotic myocardium, typically in the apical septum with anterior MI or near the base of inferior MI. The size of the defect determines the magnitude of the left to right shunt, which will affect the survival. Presentation is acute hemodynamic compromise with hypotension, biventricular failure and a new, loud, harsh, holosystolic murmur best heard at the lower left and right sternal borders. ECG may show persistent ST elevations for more than 72 hours in those not undergo reperfusion. Defects can be visualized by echocardiography and confirmed with Swan-Ganz catheterization via the measurement of a “step-up” in the oxygen saturation right atrial to pulmonary arterial. Patients with HF and shock require emergent surgical repair, while delayed surgical management is feasible in patients with HF without shock. Transcatheter closure of a post-infarction VSD is another potential approach which may be appropriate for patients who otherwise are not candidates for other surgical treatments.

3. Acute mitral regurgitation following myocardial infarction is due to ischemic papillary muscle dysfunction, LV dilatation or true aneurysm, or papillary muscle/chordal rupture. The degree of MR may vary from mild (which may be transient during ischemia) to moderate-severe MR (which may be due to papillary muscle or chordal rupture). Papillary muscle rupture is seen both in STEMI and NSTEMI, and accounts for 5% of deaths seen in AMI. It is usually seen 2-7 days post-MI and more frequently affects the postero medial papillary due to its sole blood supply from the PDA, whereas the anterolateral papillary muscle has a dual blood supply from LAD and LCx. Acute MR occurs more frequently in patients presenting with their first infarction without established collateralization and up to 50% of these patients may have only single vessel disease. Presentation is acute onset of hypotension and pulmonary edema with a hyperactive precordium and a mid-, late- or holosystolic murmur that has widespread radiation. Intensity of the murmur does not necessarily correlate with the severity of the regurgitation. As many as 50% of patients who have severe MR due to rupture have early equalization of left ventricular and left atrial pressures resulting in silent MR or a short, soft, indistinct murmur. Clinical diagnosis is confirmed by echocardiogram, which may demonstrate a flail segment of the mitral valve, a severed papillary muscle, or chordae moving freely within the left ventricular cavity. Swan-Ganz catheterization usually reveals giant v-waves. Medical treatment includes aggressive reduction of afterload using nitrates, sodium nitroprusside, diuretics and IABP counterpulsation. Emergent surgery remains the treatment of choice for papillary muscle rupture, although operative mortality is high (20-25%). Mitral valve repair is superior to replacement and should be attempted in experienced centers when there is no papillary necrosis present.

References
Case Presentation

A 35-year-old Caucasian man with Pre-B cell ALL on day 197 post allogenic stem cell transplant and with a chest tube for pneumothorax post VATS was admitted for pain at his chest tube site. Sixteen days into his admission he developed acute onset of blurry vision. The patient first noticed some difficulty reading a wall clock when he woke up in the morning followed by a subsequent worsening of his visual acuity over the next eight hours. By late afternoon he could only detect light. Review of systems was significant only for an intermittent headache over the preceding week.

The patient had a past medical history of pre-B cell ALL diagnosed one year prior, allogenic stem cell transplant six months ago, graft versus host disease, nutrition via provided by home TPN, Adenovirus infection three months ago status post IVIG and a hospitalization one month ago during which VATS was performed. The pathology from his VATS was consistent with non-specific interstitial pneumonitis. His hospitalization post-VATS was complicated by pneumothorax and required chest tube placement which was being cared for at home with the assistance of a visiting nurse.

On this admission the patient presented to an outside hospital emergency room complaining of pleuritic chest pain and increasing shortness of breath. Early in his admission he was empirically started on amphotericin B for suspected fungal etiology of his pulmonary symptoms. He was also diagnosed with gastrointestinal graft versus host disease (GVHD) for which he was being treated with steroids and immunosuppressive agents.

Medications included cyclosporine, sirolimus, hydrocortisone, Cellcept, Ambisome, Leukine, amikacin, acyclovir, vancomycin, pentamidine, Dilaudid PCA, acyclovir, Marinol, Nexium, TPN for nutrition, sliding scale insulin and Zoloft.

On physical examination the patient’s temperature was 98.3°F, respiratory rate was 16, blood pressure was 146/107 mmHg, pulse was 71 and pulse oximetry was 96% on room air. His head, neck, heart and lung examination were unremarkable. He had a chest tube to water seal. His abdominal exam was significant for an ileostomy draining brown liquid stool. While he was alert and oriented to person, place and time, he was confused and answered questions inappropriately. His speech was normal and he did not have any focal neurologic deficits. His pupils were equal, round and reactive to light, extra ocular movements could not be assessed secondary to his poor visual acuity and there were no signs of increased intracranial pressure by dilated funduscopic exam.

Laboratory studies on the day of presentation revealed a complete blood count within normal limits. Serum electrolytes and creatinine were unremarkable. Cyclosporine and sirolimus levels were within the appropriate range.

Radiographic studies

Figures 1-5 are our patient’s neuroimaging studies performed the day he presented with rapid vision loss. While there is no single pathognomonic radiographic finding for PRES, these CT and MRI images demonstrate a series of findings typically suggestive of the syndrome.

The clinical presentation above confirmed by MRI led to an early diagnosis of Posterior Reversible Encephalopathy Syndrome (PRES) in our patient. The most likely culprit was the cyclosporine he had been taking post stem cell transplant. Both his cyclosporine and sirolimus were stopped immediately. Our patient’s vision loss persisted four days after the cyclosporine and sirolimus were discontinued. On the fifth day, however, he woke in the morning reporting a dramatic, complete resolution of his visual disturbances.

Discussion

Posterior Reversible Encephalopathy Syndrome (PRES)

The classic clinical syndrome includes headache, visual changes, confusion, lethargy and seizures. The headache is typically described as constant, bilateral, moderate and dull in quality. Visual changes can progress to complete visual loss or may manifest as visual hallucinations. Funduscopic exam is usually normal as was seen in our patient. Neurologic exam rarely reveals any focal deficits. Seizures usually present as generalized tonic clonic.

Little can yet be confirmed about the incidence of or risk factors for this syndrome since a significant portion of what is known is based on published case reports. PRES is most commonly seen as a complication of hypertensive encephalopathy, eclampsia and cytotoxic and immunosuppressant medications (most notably cyclosporine, tacrolimus and interferon) but there is a long list of

Figure 1. Non-contrast CT shows bilateral hypodense foci in the parieto-occipital region consistent with tissue edema.

Figure 2. FLAIR weighted image shows high signal intensity in the occipital lobes. This sequence does not discriminate between vasogenic and cytotoxic edema. PRES is among the many causes of increased FLAIR signal.

1 Thomas Jefferson University Hospital, Philadelphia, PA
2 Hahnemann University Hospital, Philadelphia, PA
documented etiologies. These varying clinical scenarios are most clearly unified by the neuroimaging findings seen on CT scanning and MRI. While cyclosporine is the most common medication associated with PRES, it is unclear what specific trigger initiates the syndrome in any particular patient. PRES can develop within days or many months after exposure and serum levels of cyclosporine also seem to be a poor predictor of risk for the syndrome.

There are multiple hypotheses concerning the pathogenesis of PRES but most of the literature describes the syndrome as the result of impaired cerebral autoregulation and endothelial dysfunction. The most plausible hypothesis is that, as the body’s ability to maintain constant cerebral perfusion is impaired or exceeded, increases in systemic blood pressure could lead to extravasation of fluid into the surrounding tissue causing vasogenic edema. Endothelial dysfunction may also contribute since PRES seems to occur with higher frequency in patients with chronic renal failure, vasculitis, sepsis and hemolytic uremic syndrome.

Care must be taken to exclude other equally serious diagnoses such as embolic stroke, venous thrombosis, metabolic encephalopathy, encephalitis, vasculitis or demyelinating disorders. This can best be accomplished with neuroimaging including CT scanning and MRI. Most frequently seen is symmetrical white matter edema in the parieto-occipital regions as noted in Figures 1-5.

Appropriate treatment requires discontinuation of the offending agent or treatment of the underlying disease. Despite optimal care, some patients sustain permanent vision loss or epilepsy secondary to PRES. In the majority of cases, however, clinicians can expect resolution of PRES in days to weeks. Blood pressure should be tightly maintained in the normal range with titratable parenteral agents such as nicardipine or labetalol. Current guidelines for treating malignant hypertension should be incorporated into the management of the patient when applicable. Steroids are used in some settings but are not widely accepted as an appropriate treatment because of the associated risk of worsening hypertension and fluid overload. Neuroimaging will also document resolution of PRES correlating well with the patient’s symptoms. The offending agent should never be reintroduced to the patient.

The acute development of seizures, visual disturbances, headache or confusion especially in a patient with hypertension, taking immunosuppressive or cytotoxic agents or with impaired renal function should prompt an urgent CT scan and MRI to evaluate for PRES. This syndrome, while usually reversible in days to weeks following treatment of the underlying process or withdrawal of the culprit medication, has the potential to remain permanent resulting in significant disability if there is a delay in appropriate diagnosis and treatment.

References

Case Presentation
A 78 year-old man with a history of type 2 diabetes mellitus, hypertension, hyperlipidemia, seizure disorder, dementia, and alcohol abuse was admitted to the Wilmington VA Medical Center for treatment of deep vein thrombosis of the lower extremity. During the hospital course, the patient had a brief episode of supraventricular tachycardia. An echocardiogram revealed dilated cardiomyopathy, an ejection fraction of 20%, and apical and inferolateral akinesis-hypokinesis. On the following day, the patient developed cardiac arrest with ventricular fibrillation (VF) that was terminated by electric defibrillation. An electrocardiogram (Figure 1) obtained immediately after defibrillation demonstrated sinus bradycardia, a prolonged QT interval, and T-wave alternans. After the cardiac arrest, the patient was ventilator-dependant, and his family decided to withdraw life-supporting care.

Since the early 1900s, T-wave alternans (TWA), or repolarization alternans, has been linked to ventricular arrhythmias. TWA refers to the alternation of T-wave shape or timing from beat-to-beat on the electrocardiogram (ECG). TWA may also involve the ST segment or U wave but ultimately reflects T-wave changes. Note that this is still in stark contrast to electrical alternans totalis, which refers to an alternating axis or voltage of all ECG components.

Although the exact pathophysiology of TWA is unknown, it is most likely caused by a temporal heterogeneity in ventricular repolarization. This dispersion in ventricular repolarization is an important mechanism underlying ventricular arrhythmias. In essence, TWA represents an electrical state of heightened arrhythmogenicity and thus possibly a gateway to VF.

References

Figure 1. The post-cardiac arrest electrocardiogram demonstrates sinus bradycardia at a heart rate of ~40 beats per minute and a prolonged QT interval. Note the alternating T-wave morphologies most easily appreciated in leads V2-V5.
Man with Increasing Fatigue and Myalgia
Lax Gadde, MD, and Martin Kerrigan, MD

Case Presentation
A 69 year-old male with a past medical history of hyperlipidemia, GERD, and transitional cell carcinoma of the bladder currently in remission was admitted to the hospital with increasing fatigue, arthralgias, and myalgias. He noted that his symptoms began approximately four weeks prior to admission after working outside in his yard and on his swimming pool. He stated that one week later he developed red blotches on his thighs, abdomen and chest followed by arthralgias and myalgias. He noted there were ticks where he was working but could not recall a definite tick bite, nor did he find evidence of one. On further questioning he revealed that his neighbor had Lyme disease in the past, and his dog also had Lyme disease. He presented to his primary care physician three weeks later with myalgias in his arms, shoulders, elbows, and thighs bilaterally. His outpatient medication include Niaspan, omeprazole and Lipitor which he had been taking for the prior two years. Laboratory evaluation revealed a white blood count of 7000 cells per mm3, hemoglobin of 11.2 g/dL, ESR of 119 mm/hr and a serum creatinine of 1.0 mg/dL. Lyme disease was considered and serologies were sent but no antibiotics were started. The Lyme IgM result returned positive 10 days after his visit to his primary care physician, and the patient was instructed to come in to the hospital to start treatment. He was still feeling fatigued. An EKG done upon admission revealed a 2:1 AV Block (Figure 1) with a heart rate in the 40s and a widened QRS complex. The patient was admitted to telemetry for lyme carditis and was started on treatment with ceftriaxone 2 grams once daily which was continued for 2 weeks. His symptoms resolved and his repeat EKG showed sinus rhythm with a 1st degree AV Block with a HR of 78 (Figure 2). The patient’s final diagnosis was Lyme carditis due to early disseminated Lyme disease.

References
TREATMENT OF CROHN’S DISEASE IN A PATIENT WITH CONCOMITANT HEPATITIS C AND HEMOPHILIA

Donna Williams, MD

Introduction
Treatment of Crohn’s disease often involves the use of immunomodulating drugs. Most trials of these drugs have excluded patients with coexisting illness by study design. The purpose of this case report is to describe the treatment of a rare case of Crohn’s disease in the face of concomitant hepatitis C and hemophilia.

Case Presentation
The patient is a 37 year-old Caucasian male who has a history of severe factor IX deficiency complicated by frequent bleeding into joints, hepatitis C genotype 1b acquired through factor transfusions, and terminal ileal Crohn’s disease which was diagnosed by small bowel x-ray in 1985. At that time, he was treated with azulfidine and corticosteroids with some improvement. The patient was maintained on 5-ASA and steroids until 2000, when steroids were tapered in an attempt to prepare him for treatment of his hepatitis C. By May 2001, the patient was off all steroids and was maintained on asacol 1200 mg BID. At that time, liver biopsy revealed liver parenchyma with focal, mild to moderate macrovesicular steatosis. Portal tracts had mild, lymphocytic infiltrate and bile ducts were present without significant epithelial atypia. Due to the benign findings on liver biopsy, the decision was made to defer treatment of hepatitis C.

In the fall of 2001, the patient began to experience episodes of bright red blood per rectum, attributed to flares of his Crohn’s disease, which required treatment with steroid pulses and factor IX infusions. Ultimately, the patient was placed on daily alternating doses of prednisone 20 mg and 50 mg. In January 2002, he presented to his hematologist and subsequently to the ED with hematochezia and hemoglobin of 6.4 g/dL. Colonoscopy revealed aphthous ulcerations in the terminal ileum consistent with Crohn’s disease. The bleeding was stopped with factor IX infusions and IV solumedrol. After three days the patient was discharged on budesonide 9 mg daily, Asacol 3.5 g daily, and was also receiving daily injections of factor IX. Despite these efforts, he continued to bleed and required iron infusions for his profound iron deficiency anemia. Eventually, the patient’s Crohn’s disease was under control with alternate day prednisone at 30 mg.

The patient was doing well until December of 2003, when he again began experiencing bright red blood per rectum. He was started on azathioprine 50 mg, which was soon discontinued secondary to patient intolerance. Steroids were increased to a daily dose of prednisone 40 mg with only mild clinical response. In May 2004, the patient was requiring factor IX infusions approximately once a month for recurrent GI bleeding. In October 2004, after discussion with the patient’s hematologist and Centocor (producers of Remicade), the decision was made to treat the patient with remicade at the standard dose of 5mg/kg at weeks 0, 2, and 6 weeks. Initially, the patient responded well with decreased GI complaints, and he achieved remission of his Crohn’s disease after the third dose. He no longer had any GI bleeding and his hemoglobin stabilized at 15.3 g/dL. His prednisone dose was able to be tapered to 20 mg every other day; further tapering is in progress. After seeing these results, the patient was continued on the maintenance dose of 5 mg/kg every 8 weeks.

Discussion
Review of the literature revealed the absence of reports of patients with concomitant Crohn’s disease, hemophilia, and hepatitis C. The literature consists of information about patients who suffer from hemophilia and hepatitis C as a result of transfusion acquired disease, but there are no cases also involving inflammatory bowel disease. Indeed, one study performed by Thompson, et al.1 showed that the incidence of inflammatory bowel disease among patients with hemophilia and von Willebrand’s disease is lower than that found in the general population. Of 6433 patients with hemophilia and 3129 patients with von Willebrand’s disease, only 4 cases of Crohn’s disease were detected while the expected number of cases was 11.97-16.58. This study suggests that thrombotic events play a role in the development of inflammatory bowel disease, and therefore, hemophilia protects against IBD.2

Although there are a large number of patients who have Crohn’s disease who are also infected with hepatitis B and/or hepatitis C as a result of frequent endoscopic and surgical procedures, there are relatively few reported cases of patients with HBV or HCV who have been treated with infliximab (Remicade, Centocor) for control of Crohn’s disease.3 Infliximab is a monoclonal antibody directed against tumor necrosis factor alpha (TNF α), which is a proinflammatory agent. TNF α is present in abnormally increased amounts in inflammatory liver diseases such as chronic hepatitis B and C as well as autoimmune and alcoholic hepatitis. It has been suggested that up regulation of TNF α may encourage clearance of hepatitis B virus.4 Therefore, it has been postulated that treating patients with concomitant hepatitis B or C and Crohn’s disease with infliximab would increase the amount of circulating virus and induce reactivation. Even so, the overall consensus in the literature until recently was that immunomodulating drugs used for the treatment of Crohn’s disease did not alter the course of patients with coexisting hepatitis B or hepatitis C.5

In 2004, two case reports addressed this issue among four cases of patients with hepatitis B and Crohn’s disease. These four patients were treated with infliximab in standard doses of 5 mg/kg, and two of them experienced acute flare of chronic hepatitis B after withdrawal of infliximab therapy.6 7 One of these patients died as a result. The two patients who did not experience a flare of hepatitis B had been treated with lamivudine 100 mg daily during treatment, which supports its use to prevent reactivation of hepatitis B. Among three cases of patients with concomitant...
hepatitis C and Crohn’s disease who were treated with infliximab in standard doses, none experienced reactivation of hepatitis C.\textsuperscript{5,9}

After review of the literature and discussion of treatment strategies with hematology, hepatology, and Centocor, the decision was made to treat our patient with infliximab due to the frequency and severity of his Crohn’s disease flares. The patient’s encouraging response to infliximab has supported the claim that infliximab is safe in patients with hepatitis C and hemophilia without adverse effects on either concomitant illness.

References
Case Presentation
A 55 yr old male with past medical history significant for end stage liver disease, intravenous drug abuse and hypertension presents to the ED with complaints of bright red blood per rectum for the past 3 days and non-specific chest discomfort. Medications on admission were amlodipine, valsartan /HCTZ, xanax, terazosin, and high dose methadone maintenance therapy.

On admission, temperature was 98º F, heart rate was 50, respiratory rate was 18, blood pressure was 122/75, and oxygen saturation was 99% on room air. Physical examination was normal. No bright red blood per rectum was noticed and stool was heme-negative. Initial laboratory values including a complete blood count and chemistry panel were within normal limits including a hemoglobin of 14.6, calcium of 9.6, potassium of 3.9, and magnesium of 1.8. The patient was ruled out for myocardial infarction with three negative troponins. The admission EKG is presented below (Figure 1).

While in the ED on the day of admission, the patient was noticed to have ventricular tachycardia on telemetry. He was asymptomatic during the episode and his vital signs were stable. The telemetry strip at that time is shown below (Figure 2).

The patient was given 2 grams magnesium in the and the patient was admitted to the CCU. QT interval prolongation from high dose methadone therapy was the most likely cause of his episode of polymorphic ventricular tachycardia. Electrophysiology consultation recommended that his methadone dose be decreased so that his QT interval would be within normal limits. Prior to discharge, his methadone dose had been lowered without any symptoms of methadone withdrawal and his EKG on discharge is shown below (Figure 3).

Discussion
The long QT syndrome is a disorder of myocardial repolarization characterized by a prolonged QT interval on the electrocardiogram. This syndrome is associated with an increased risk of a characteristic life threatening cardiac arrhythmia known as Torsades de pointes. Torsade de pointes is a form of polymorphic ventricular tachycardia that occurs in the setting of acquired or congenital QT interval prolongation. Polymorphic ventricular tachycardia is defined as a ventricular rhythm faster than 100 beats/min with frequent variations of the QRS axis, morphology or both. The peaks of the QRS complexes appear to twist around the isoelectric line of recording; the name literally translates to “twisting of the points.”

The most common causes of acquired long QT interval syndrome are either medication-induced or electrolyte abnormalities. Some medications known to cause QT interval prolongation are antiarrhythmics such as quinidine, procainamide, disopyramide, amiodarone, dofetilide, and ibutilide; antibiotics including erythromycin, clarithromycin, and fluoroquinolones; antihistamines such as terfinadine and astemizole; the antipsychotic agents chlorpromazine, haloperidol, and thioridazine; and high dose methadone. Caution should be used when prescribing a drug that prolongs QT interval in patients with risk factors; a baseline EKG and daily EKGs should be obtained during the course of therapy. There are various risk factors for drug induced torsades including female sex, hypokalemia, hypomagnesemia, bradycardia, rapid rate of intravenous infusion with a QT interval prolonging drug, congestive heart failure, baseline QT interval prolongation; sub clinical long QT interval prolongation, and ion channel polymorphisms.
QT prolongation and torsade de pointes have been reported in patients on high doses (100 to 400 mg) of methadone. Methadone has a long plasma elimination half life and is metabolized by the CYP3A4 enzyme system in the liver, so any drug which inhibits the CYP3A4 enzyme system can increase methadone levels in the blood. CYP3A4 inhibitors include antimicrobials, antifungals, statins, and acetaminophen. Two mechanisms can explain the association between methadone and torsade de pointes, synthetic opioids cause bradycardia and they can inhibit the outward potassium current during phase 3 of action potential.

In a retrospective analysis of reports of adverse events associated with methadone from 1969 to 2002 found that out of a total of 5,503 adverse events associated with methadone, 43 (0.78%) were reported to be torsades de pointes and an additional 16 were noted to have QT prolongation. The dose reported was 410+/-349 mg/day (median 345 mg, range 29-1680) while only 10 cases were within the recommended range for methadone maintenance (60-100mg). Female gender, interacting medications, hypokalemia, hypomagnesemia and structural heart disease were found in 44 (75%) cases. Most adverse events required hospitalization (28/59) and death resulted in 5 cases.

References
CASE REPORTS

WOMAN WITH AIDS AND STATUS EPILEPTICUS

Bonnie Callahan, MD

Case Presentation

A 42 year-old female with a medical history of HIV presented to the Emergency Department with nausea and vomiting for the past five days. Six days prior to presentation, she had one week of symptoms of progressive dyspnea and non-productive cough which were evaluated by her primary care physician. At that time, blood work revealed a CD4 count of 150 cells/mm3 and a chest x-ray was suggestive of pneumonia. She was given a prescription of trimethoprim-sulfamethoxazole (TMP/SMX) and guaifenesin with codeine. Within twenty-four hours of starting the prescribed medications, she developed nausea and vomiting, and she stopped taking both medications three days prior to presentation. Although her cough and shortness-of-breath were much improved, her nausea and vomiting had not improved with discontinuation of the TMP/SMX and guaifenesin with codeine. She reported she was unable to tolerate any solid foods and was only tolerating small amounts of liquids. She also noted some associated epigastric “crampiness.” Review of systems was notable for a new headache that started the morning of presentation to the hospital. The headache was bilateral, frontal, and “achy, non-throbbing.” She had no associated photophobia, vision change, or neck-stiffness. She reported no fever, chills, chest pain, hemoptysis, diarrhea, or constipation. She had no other complaints.

On review of the patient’s past medical history, she was noted to have type 2 diabetes, hypertension, “mild” asthma (never requiring hospitalization or intubation) and HIV/AIDS with a recent CD4 count of 150 cells/mm3. Her surgical history included a TAH-BSO and breast biopsy. She was allergic to penicillin, which caused anaphylaxis. Her medications included glipizide, amlodipine, losartan, hydrochlorothiazide, and albuterol. Social history was negative for tobacco, alcohol, or substance abuse. The patient worked in an office setting and lived at home with her daughter. She reported no recent sick contacts and no recent travel. Her family history was significant for type 2 diabetes in her mother, who died from a stroke at age sixty, and breast cancer in her sister, who died from a stroke in her fifties.

In the ED, the patient was afebrile and her vital signs included a heart rate of 92 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 132/62 mmHg, an oxygen saturation of 98% on room air. She was alert and oriented and in no acute distress. Physical exam revealed oral thrush and scattered expiratory wheezes in bilateral lungs with decreased breath sounds at bilateral bases. Her abdomen was diffusely tender, with normoactive bowel sounds throughout and no rebound or guarding. No masses or organomegaly were appreciated. The physical exam was otherwise unremarkable.

The initial evaluation included a chest x-ray which showed “hilar lymphadenopathy with upper lobe interstitial lung disease” which was thought to be secondary to infectious etiology. Her urinalysis was negative for infection, and a complete blood count showed a normal white blood cell count, a normal platelet count, and mild anemia with hemoglobin of 12 g/dL. She had an elevated lactate dehydrogenase of 287 IU/L. Her blood chemistries were normal, with the exception of a creatinine of 2.0 mg/dL, with a known baseline of 0.8 mg/dL one year earlier. Blood and sputum cultures were collected. The patient was diagnosed with community-acquired pneumonia and was started on moxifloxacin in the ED. She was also started on intravenous TMP/SMX for possible PCP and fluconazole for her oral thrush. She was admitted to the hospital and started on intravenous fluid resuscitation.

The first night of the patient’s hospital stay was uneventful. The following morning she was noted to have acute mental status change. She appeared awake, but would not answer questions or follow commands. She had a low grade temperature of 100°F, was tachycardic at 110 beats per minute, with a blood pressure of 132/62 mmHg, a respiratory rate of 20 breaths per minute, and an oxygen saturation of 99% on room air. Her physical exam was unchanged from the previous day with the exception that she could not cooperate for the neurologic exam. Her pupils were equal and reactive to light. She did grimace in reaction to painful stimuli. Her muscle tone was noted to be normal with no rigidity. She was spontaneously moving all four extremities, but not on command. The patient was transferred to the telemetry floor and a full neurologic evaluation was initiated. A lumbar puncture was planned, cultures were obtained, and a head CT was unremarkable, showing no intracranial hemorrhage, acute territorial infarct, or cerebral edema. Additionally, no mass effect or midline shift was seen on the CT scan. The patient’s fever increased to 103°F, and the infectious disease specialist saw her in consult.

The patient’s condition remained unchanged until 4:45 am the next morning, when a nurse witnessed the patient having tonic-clonic seizure activity. During the seizure the patient foamed at the mouth and desaturated to 81% on 2L oxygen by nasal canula. She continued to seize despite 6mg intravenous lorazepam and an intravenous fosphenytoin load. She was intubated and transferred to the intensive care unit on the neurology service for management of status epilepticus. In the intensive care unit she was given intravenous fosphenytoin and propofol. A lumbar puncture was performed for suspected encephalitis. Cerebrospinal fluid analysis, including evaluation for cryptococcus and herpes simplex virus, revealed no abnormalities. An MRI of her brain showed no acute abnormalities, and a work-up for an infectious etiology of her illness was negative. The infectious disease consultant suspected that the patient’s seizures were a reaction to the moxifloxacin. It was discontinued and within twenty-four hours her seizures stopped. An EEG was performed the day after her seizure activity and intubation. The EEG showed diffuse 2-6 Hertz slowing secondary to sedation. No seizure or epileptiform abnormalities were seen. Three days after her initial intubation, she was successfully weaned from the ventilator. Her mental status quickly returned to baseline. Treatment with azithromycin was initiated for her respiratory infection, and at the recommendation of the neurologists, she was maintained on anti-epileptic medications.
medication. Her hospital course was complicated by an upper extremity DVT during her stay in the intensive care unit. Ten days after her initial admission she was discharged to her home with an outpatient enoxaparin bridge to warfarin. She was instructed to follow-up with her primary care provider, neurology, and infectious disease as an outpatient.

**Discussion**

In the absence of infectious or structural etiologies of the seizures, they were likely referable to moxifloxacin hydrochloride administration. Moxifloxacin is a normally well-tolerated fluoroquinolone antibiotic used to treat community-acquired pneumonia, sinusitis, and other bacterial infections. It does not require dose-modification for renal or hepatic impairment. Some common side-effects of moxifloxacin include upset stomach, vomiting, diarrhea, dizziness, and headache. The product information supplied with Avelox (brand name for moxifloxacin) notes that seizures are a rare complication of quinolone use, and have been reported with Avelox. It reports to “use moxifloxacin with caution in patients with known or suspected CNS disorders (for example, severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold.”

Moxifloxacin has previously been reported in the literature as being associated with both seizures and status epilepticus. One case report described an elderly patient with a past history of idiopathic seizures who developed status epilepticus four days after initiating moxifloxacin treatment for a respiratory infection. His seizures stopped with discontinuation of the drug, but unfortunately he subsequently died of multiorgan failure associated with his illness. Additionally, an editorial noted that the WHO Adverse Reactions database contained 53 reports of convulsions associated with moxifloxacin.

This report provides further evidence that moxifloxacin should be avoided, if possible, in patients with a history of seizure disorders. Furthermore, moxifloxacin should be considered as the possible cause of new onset seizures in a patient who has initiated treatment with this drug.

**References**

WOMAN WITH POLYURIA AND POLYDIPSIA
Jeffrey Clough, MSIV, and Andrew Rose, MD

Case Presentation
A 20 year-old Caucasian female with a past medical history significant only for occasional headaches and anemia presents with a chief complaint of increasing thirst for two weeks. The patient was in her usual state of health until approximately two weeks prior to admission when she noted the gradual onset of increasing thirst and began drinking more and more water over the next few days. Her thirst increased to the point where she drank an estimated 18 liters of fluid during the 24 hours prior to admission. This thirst was accompanied by frequent urination, which would often awaken her during the night and she noted her urine to be very clear. These symptoms began within a few days of a vaginal yeast infection, for which she was treated with one dose of fluconazole. She denied any other symptoms during this episode.

Her past medical history was significant for occasional non-focal headaches without aura or specific precipitants. These headaches had been present for several years and responded well to NSAIDS. She also reports that she has a history of anemia and occasionally takes iron supplements. She does not report taking regular medications and has never had surgery. Her last menstrual period was approximately three weeks earlier. She is a college student, works part-time in a pharmacy and lives with her family and claims to be happy with her life. She is in a monogamous relationship with her boyfriend and reports no problems. She denies alcohol, cigarette, or illicit substance use. Her family history is significant only for hypertension, diabetes mellitus, and stroke on her maternal side and gastric cancer in her maternal grandfather. She denies any neurologic, psychiatric, or autoimmune disease in the family.

On physical examination, the patient appeared comfortable, well-hydrated, and her vital signs were normal. Her examination revealed no abnormalities, with the exception of hippus of the pupils. Full neurologic examination was normal including visual fields testing with confrontational visual fields. Initial laboratory examination revealed a mild microcytic anemia with a hemoglobin of 11.9 g/dL and a normal chemistry panel including a serum sodium of 139 meq/dL and creatinine of 0.5 mg/dL.

Differential Diagnosis and Evaluation
The most likely diagnoses given this patient’s history are diabetes insipidus (DI) or psychogenic polydipsia. DI can be further classified into nephrogenic or central. Nephrogenic DI is less likely in this case as it generally occurs either as a genetic disease presenting early in life in males or as a side effect of medications such as lithium or demeclocyline. It may also be secondary to hypercalcemia, which was normal on her laboratory evaluation. Therefore, central DI and psychogenic polydipsia were the remaining likely diagnoses. Both of these disorders are common to the patient’s demographic. Central DI is caused by destruction of the vasopressin producing cells in the posterior pituitary gland. It is most often an idiopathic phenomenon likely to be autoimmune, but other causes include infiltrative disorders such as hemochromatosis and sarcoidosis, as well as pituitary neoplasms. Psychogenic polydipsia is also idiopathic and is thought to be caused by dysfunction of thirst-regulating nuclei in the hypothalamus. It is often associated with patients who have a psychiatric disorder but can occur with infiltrative disorders and in otherwise normal patients. Psychogenic polydipsia differs from DI in that patients are driven to drink water and they urinate to compensate for the increased volume load whereas in DI patients cannot concentrate their urine and must drink to replace the lost fluids.3

The primary method to distinguish between these three disorders is the water deprivation test. In this test, the patient remains NPO and urine osmolality is measured every hour. Additionally, the serum osmolality and sodium level are measured every 2 hours. The test is stopped if the patient’s urine is concentrated to a level of 600 mOsm in which case DI is ruled out. If the serum osmolality exceeds 295 mOsm or the urine osmolality is stable for 2-3 consecutive hours (less than 10% increase) while the serum osmolality is rising, DI is the likely diagnosis. At this point, 5 - 10 mcg of vasopressin is injected subcutaneously and the urine osmolality is measured one hour later. If the urine osmolality increases by 50% or more, the patient is considered to have central DI. In many cases of central DI, the disease is only partial and can be diagnosed if the urine osmolality increases by 15-50%.4 If the patient has nephrogenic DI, the urine osmolality should not significantly increase.

In addition to water deprivation test, MRI of the brain should be obtained to rule out any obvious causes of central DI such as a mass. In idiopathic central DI, the characteristic finding on MRI is loss of the pituitary bright spot and thickening of the pituitary stalk. If central DI is determined, a pituitary panel should be obtained to rule out any other pituitary dysfunction.

The results of the water deprivation test in this patient are shown in Table 1. The patient was unable to concentrate her urine greater than 250 mOsm at 6 hours even though her serum osmolality rose to 297 mOsm after 4 hours. This indicated that she had diabetes insipidus rather than psychogenic polydipsia. She was given 5 mcg of subcutaneous vasopressin and her urine osmolality rose to 349 mOsm. Although this did not fulfill the 50% increase requirement, it did surpass the 15% requirement for partial central DI. With the high pretest likelihood of central DI rather than nephrogenic DI, it was felt that she had partial central DI. Interestingly, the patient reported a complete resolution of her symptoms of thirst following administration of vasopressin. In addition, MRI revealed loss of the posterior hypophyseal bright spot and thickening of the pituitary stalk consistent with central DI. She was started on 10 mcg of nasal desmopressin twice daily and discharged the next day with instructions to obtain outpatient blood work to monitor her electrolytes in one week and follow up with the endocrinologist in 2 weeks. A pituitary panel was drawn during the hospital stay with the results to be followed by her endocrinologist.
Discussion
Idiopathic DI accounts for 30-50% of cases of central DI. Autoimmunity is thought to be an important cause of idiopathic central DI. Pivonello et al. found that patients with idiopathic central DI were significantly more likely than control patients to display antibodies to arginine vasopressin-secreting cells. Age less than 30, known autoimmune disease, and radiological evidence of pituitary stalk thickening were all independent risk factors for having a positive antibody assay. A patient with idiopathic DI and all of these criteria has a 99% chance of having these antibodies. This patient had two of these parameters, which placed her at an 80% chance of having these autoimmune antibodies. While there is no definitive proof that these antibodies are the cause of central DI, this is a plausible explanation given our understanding of autoimmunity.

To our knowledge, there are no known case reports of an association between vaginal yeast infections or fluconazole and central diabetes insipidus. The coincidental timing and likely autoimmunity of this patient’s disease may suggest either the yeast infection or fluconazole treatment as a possible trigger for the disease. Although this represents only one case of central DI following a vaginal yeast infection with fluconazole treatment, further such reports might allow researchers to study and understand this interesting disease.

References:

Table 1. Water deprivation test

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<tr>
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<td>288</td>
<td>269</td>
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* 5 mcg vasopressin administered at this time.
Persistently Elevated Troponin Levels with a Negative Cardiac Workup: Now What?

Pamela Cines, MD

Case Presentation
A 44 year-old female with a past medical history significant only for iron deficiency anemia and syncope presented to an outside hospital with abdominal pain. The patient initially noted the pain while shopping; she described it a sharp sensation, regionalized to the right-epigastric region. When the pain recurred with greater intensity an hour later now with resulting nausea and right-arm radiation, she proceeded to her nearest ED.

Her medical history was significant for iron deficiency anemia, which with she was diagnosed during pregnancy. She had a recent hospitalization for syncope and reported positive cardiac enzymes, however she had a normal cardiac stress test. Surgical history was significant for an uncomplicated caesarian section. She reports having no allergies to medicines and her only medications are a daily aspirin and ibuprofen as needed. Social history was notable only for a five pack-year history of smoking; she quit approximately five years prior to admission.

At the OSH, physical examination was reported to be unremarkable. Her laboratory data showed a hemoglobin level of 9 g/dL, a normal chemistry panel and a troponin of 1.46 ng/mL. EKG demonstrated normal sinus rhythm without any ischemic changes. CT scan and ultrasound of her abdomen were performed and were unrevealing. The patient was transferred to TJUH for further evaluation of her troponin elevation.

On admission to TJUH, the patient was afebrile with a heart rate of 58, a blood pressure of 96/31 mmHg without evidence of orthostasis, respirations of 16, and oxygen saturation of 98% on room air. She was oriented and in no distress. Physical exam was pertinent for clear lungs on pulmonary auscultation; no jugular venous distension, pedal edema, diminished pulses, or extra heart sounds on cardiovascular examination; minimal tenderness in the right upper quadrant, a well-healed caesarean section scar, but otherwise a benign abdominal examination. Hemoccult examination of the stool was negative. The EKG performed on admission to TJUH again demonstrated normal sinus rhythm, heart rate 55, without evidence of ST-T wave abnormalities.

Laboratory evaluation again showed a microcytic anemia with an iron saturation of 4% and a troponin of 1.48 ng/mL. Transthoracic echocardiogram demonstrated an ejection fraction of 65% with no contraction abnormalities or evidence of valvular disease. Cardiac catheterization was performed revealing no evidence of occlusive coronary artery disease. Gastroenterology consult was obtained for evaluation of her abdominal pain. The patient underwent a right upper quadrant ultrasound and upper endoscopy, both of which were normal.

The patient remained symptom-free throughout her three-day hospitalization at TJUH, she was discharged to home in stable condition. Curiously, her troponin level on day of discharge remained elevated at 1.48 ng/mL.

Discussion
Cardiac troponins are regulatory proteins controlling the interaction between actin and myosin mediated by calcium. In most normal subjects, cardiac troponins are completely undetectable. Troponin levels will begin to rise in 4 to 6 hours after an acute insult to cardiac tissue—usually related to lack of blood flow—and will remain elevated for up to 10 days, permitting late diagnosis.

In Western Medicine, and especially in Emergency Medicine, any level of detectable troponin is typically regarded as the sine qua non of an acute coronary syndrome. Indeed, according to the ACC/ESC consensus document, “any amount of myocardial damage implies an impaired clinical outcome for the patient” and that there is “no discernible threshold below which an elevated value of cardiac troponin would be deemed harmless. The ACC/AHA guidelines do indicate that myocardial necrosis as reflected by elevated troponin levels may not be due to coronary artery disease; and thus a diagnosis of myocardial ischemia, or infarction, should be supported by additional clinical and electrocardiographic evidence.

While myocardial ischemia may imply elevated troponin levels, the converse is not always true. Disease states such as sepsis, atrial fibrillation, CHF exacerbation, pulmonary embolism, myocarditis, myocardial contusion, and renal failure are also associated with detectable troponin.

In 2002 Bakshi et al enrolled 21 consecutive patients with elevated troponin who had either normal coronary angiography or stenosis of less than 50% without complex features or thrombus. Among the enrollees troponin elevations ranged from 0.21 to 54.79. Following unrevealing angiography, patients were classified as to the likely cause of their elevated troponin. Eleven of the 21 patients had tachycardia, strenuous exercise, CHF, and pericarditis ascribed to the cause of their elevated troponins. For the remaining 10 patients, however, no clear precipitating event could be identified.

More importantly, a study by Ng et al reviewed 1000 consecutive patients presenting to a large, suburban hospital ED. One hundred and twelve of these patients had elevated troponin levels, but amazingly, 45% of them had a final diagnosis other than acute coronary syndrome. These statistics suggest that measuring troponin is a highly sensitive—but not a highly specific—test in settings of a low pretest probability.

This case review will discuss the differential diagnoses of elevated cardiac troponin when acute coronary syndrome has been excluded.

1. Demand ischemia refers to a mismatch between myocardial oxygen demand and supply. Myocardial oxygen demand increases in the setting of tachycardia, increased afterload, systemic inflammatory response syndrome (SIRS), sepsis, and septic shock. Decreased oxygen delivery can occur in tachycardia, hypotension, and hypovolemia. Each of these conditions is either
caused by, or leads to, tachycardia, a situation in which myocardial oxygen demand increases and supply decreases. In tachycardia the myocardium requires more oxygen to maintain its increased contractile rate; however, diastolic time also shortens, which has a net effect of limiting blood flow to the coronary arteries, thereby limiting oxygen supply. In the case of hypovolemia or hypotension, there is reduced perfusion pressure during systole, also leading to decreased oxygen supply to the myocardium. This set of circumstances can result in the release of cardiac troponin into circulation.

2. Sepsis is another clinical situation in which physicians often detect elevations of cardiac troponin. Amman et al studied 20 septic ICU patients, 17 of whom were noted to have elevated troponin levels. Troponin measurements ranged from 0.17 to 15.4. Ten of these patients had no history of coronary artery disease (CAD). Of the five patients who subsequently expired, eighty percent had no demonstrable CAD on post mortem. This study suggests that elevations of cardiac troponin in the setting of sepsis is not uncommon, and may occur in patients who otherwise show no evidence of CAD. The mechanism of troponin release in the setting of sepsis has not been completely elucidated. Endotoxin release from gram-negative organisms has been shown to lead to ventricular dilatation and myocardial depression. However, in Amman's study the majority of patients had gram-positive sepsis. It has been postulated that troponin release in sepsis may be due to increased membrane permeability. One possibility is that cytokines and interleukins released during sepsis cause the degradation of troponin to smaller, low molecular weight forms which are release through a more permeable membrane.

3. Left ventricular hypertrophy is also on the differential for elevated troponin. Hamwi et al measured troponin levels in 207 consecutive patients referred for echocardiogram. After excluding 124 on the basis of acute coronary syndrome and 29 on the basis of suboptimal echocardiogram, Hamwi’s group determined that 8 of 74 patients had troponins out of the normal range. These 8 patients had a significantly higher mean left ventricular mass as compared to those with normal troponin levels. One hypothesis proposed in the article suggested that increased muscle mass would invariably result in increased oxygen demands. Furthermore, the increased muscle mass would potentially lead to decreased flow reserve secondary to “remodeled coronary microcirculation.” Although intriguing, this article represents, at best, a correlation between enlarged muscle mass and troponin elevation, and is far from a rigorous proof of causality. Indeed, as Hamwi’s group itself concludes, “[w]hether patients with combined troponin-I elevation and LV hypertrophy represent a subgroup with a higher risk of adverse cardiovascular outcome needs to be further determined.”

4. Myocardial strain results when the myocardium is subjected to volume or pressure overload as in the case of congestive heart failure, damage to myofibrils may occur. A correlation has been demonstrated between elevated troponin and BNP levels in this setting as well as between myocardial stretch and apoptosis. Increased wall stress may also lead to decreased subendothelial perfusion, resulting in troponin release and decreased left ventricular function. Elevation of troponin tends to be associated with worse outcomes. In chronic heart failure, activation the sympathetic nervous system and inflammatory cytokines by the renin-angiotensin system may lead to myocyte injury and death, thus explaining elevated troponin levels in this setting. It is worth noting that troponin elevation is evident in up to 50% of people with a diagnosis of acute pulmonary embolism. Although not useful for diagnosis, the presence of an elevated troponin level in the setting of pulmonary embolism does portend a worse prognosis, as it suggests a significant clot burden against which the heart is unable to pump.

5. Other causes include vasospasm, trauma, pericarditis, myocarditis and renal failure. Vasospasm, or Prinzmetal’s angina, can produce prolonged periods of ischemia, leading to the release of troponin in the absence of myocardial necrosis. Similarly, vasospasm has been offered as a possible explanation for elevated troponin in normal subjects following extended periods of exercise. Troponin rise has also been documented in cases of ischemic strokes and subarachnoid hemorrhage. Additionally, troponin is released in a significant number of people who incur blunt thoracic trauma. Hasdamir et al measured cardiac troponins in 35 patients who were hospitalized following ICD shocks. They demonstrated that troponin levels are elevated in the majority of patients who receive multiple shocks from their ICD, but only a small percentage of the elevations are due to an acute coronary syndrome. Elevation of troponin can also be seen in acute pericarditis and myocarditis as well as chronic renal failure.

Conclusion
In this patient none of the aforementioned causes could sufficiently explain her persistent elevation of troponin. It is clear, though, that given the multiple potential causes of troponin elevations outside of acute coronary syndrome, an individual’s clinical presentation needs to considered thoroughly before patients are subjected to expensive—and potentially risky—diagnostic studies.

References
ANOMALOUS ORIGIN OF LEFT CIRCUMFLEX ARTERY FROM THE RIGHT CORONARY ARTERY

Sivakumar Srinivasan, MD, and Sandeep Anreddy, MD

Case Presentation
A 56 year-old male with past medical history significant for diabetes and obesity presented for an elective diagnostic cardiac catheterization. The catheterization films are shown below (Figures 1 and 2).

Discussion
Adult coronary anomalies are not very common and are usually casual findings of diagnostic angiographic studies. The incidence of these anomalies has been reported to be between 0.29-1.34%. Although coronary artery anomalies are far less common than acquired coronary artery disease, their impact on premature cardiac morbidity and mortality among young adults is not trivial. In a study of 126 nontraumatic sudden deaths in young adults, cardiac abnormality was found in 64 cases (51%), with coronary artery abnormalities being the most common cardiac abnormality (61%).

Coronary artery anomalies can be classified as hemodynamically significant or insignificant. Hemodynamically significant anomalies of the coronary arteries are characterized by abnormalities of myocardial perfusion, which lead to an increased risk of myocardial ischemia or sudden death. These anomalies include an anomalous origin of either the LCA or the RCA from the pulmonary artery, an anomalous course between the pulmonary artery and the aorta (interarterial) of either the RCA arising from the left sinus of valsalva or the LCA arising from the right sinus of valsalva, occasional myocardial bridging, and congenital coronary artery fisula.

Anomalous origin of the coronary artery from the pulmonary artery (ALCAPA) is one of the most serious congenital coronary artery anomalies. It has an estimated prevalence of one in 300,000 live births. Most affected patients show symptoms in infancy and early childhood. Approximately 90% of untreated infants die in the 1st year of life, and only a few patients survive to adulthood. In the most common form of this disease, the LCA arises from the pulmonary artery and the RCA arises normally from the aorta (Bland-White-Garland syndrome).

The four recognized patterns of an anomalous origin of a coronary artery from the opposite or noncoronary sinus are (a) the RCA arising from the left coronary sinus, (b) the LCA arising from the right coronary sinus, (c) the LCx or LAD artery arising from the right coronary sinus, and (d) the LCA or RCA (or a branch of either artery) arising from the noncoronary sinus. A coronary artery arising from the opposite or noncoronary sinus can take any of four common courses, depending on the anatomic relationship of the anomalous vessel to the aorta and the pulmonary trunk: (a) interarterial (ie, between the aorta and the pulmonary artery), (b) retroaortic, (c) prepulmonic, or (d) septal (subpulmonic). It is of great clinical importance which course is taken, an interarterial course carries a high risk for sudden cardiac death. The most common course of an anomalous RCA arising from the left sinus of Valsalva is interarterial; this variant can be associated with sudden cardiac death in up to 30% of patients. It has been postulated that, when dilation of the aorta occurs during exercise, the anomalous slit-like ostium for the RCA in the left sinus becomes narrower, possibly limiting coronary blood flow and resulting in myocardial infarction. The LCA arises from the right sinus of valsalva in 0.09%–0.11% of patients who undergo angiography, an interarterial course may be seen in up to 75% of patients with this anomaly.

Anomalous origin of the Left circumflex artery (LCx) from the proximal right coronary artery (RCA) is one of the most common forms of coronary artery anomalies. It has been reported in 0.17%–0.4% of patients undergoing coronary angiography. In almost all cases where the LCx arises from the proximal RCA the course is retroaortic. Results from the coronary artery surgery study showed that anomalous circumflex coronary arteries had a significant greater degree of stenosis when compared to non-anomalous arteries (p=0.02) though there was no significant difference in survival by location or degree of stenosis in the anomalous artery at 7 years.

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