

In House

An Internal Medicine Resident Journal

Issue 1

May 2011



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Dedicated to Dr. Susan Wolfsthal
Internal Medicine Residency Director

Letter from the Editors

Issue 1

May 2011

Neda Frayha, MD and Elizabeth Lamos, MD

We are so proud to bring you this very first issue of "In House." We are dedicated to highlighting and promoting the creative and scholarly work of our talented residents. What better forum than an internal resident journal? We recognize that some residents excel at prose while others prefer analytic writing, and we hope to embrace this very diversity of styles and perspectives in our new journal. Residents from all post-graduate years in our categorical and combined programs volunteered the pieces you'll see in this inaugural issue - a testament to the enthusiasm and range of our Internal Medicine program.

Our early expectations were quite modest, but the residents exceeded our boldest hopes. Initially we worried about how we would even fill our pages. Our fears evaporated as the submission count rose higher and higher. We are proud to bring you three *Clinical Vignettes*, three *Images in Medicine*, a fantastic and timely *Viewpoint* on work hours, two *Expressions* pieces, and review articles by two graduating residents. It is particularly exciting to present these senior review papers to a wider audience given the time and effort poured into each manuscript. Every graduating resident is required to deliver a senior talk, consisting of both a 45-minute oral presentation and a comprehensive review paper, on a topic of their choice. Here we showcase two senior talks that are particularly well researched and clinically relevant to our practice of both inpatient and outpatient medicine.

We are equally and deeply passionate about the personal and reflective pieces in the pages ahead of you. It was important to us to provide a venue for our residents to reflect on current issues and experiences that shape their view of medicine and the world around them. Residency is filled with intense shared moments : moments of humor, joy, frustration, and fear; moments when we grow together as physicians. We share these crucial years of our own development with each other. We include these *Viewpoint* and *Expressions* pieces to add to this shared experience, to reveal dimensions of our colleagues that we may not otherwise get to know.

We would like to thank each of the senior physicians who provided feedback, editing expertise, and encouragement to the residents. We enjoyed our role in the editing process, but our ultimate goal was to facilitate dialogue and scholarly discussion between residents and faculty. Sometimes there is no better learning experience than that of the mentor-mentee relationship.

We hope that you find this journal an exciting and informative adjunct to our resident research forum, senior talks, annual ACP Associates' meeting, and mentoring program. Thanks to Leor Jaffe for his suggestion to title the journal "In House." We are already looking forward to the next issue and the opportunity to continue collaborating with our residents and faculty. Enjoy!



Clinical Vignette: Hemoglobin Zurich

Issue 1

May 2011

Owen Debowy, MD, PGY-3 in Internal Medicine and Pediatrics

Jason Incorvati, MD, PGY-2 in Internal Medicine

PRESENTATION

A 21-year old woman with a familial hemoglobinopathy presented with fatigue, lightheadedness, and shortness of breath for one week. She described a decrease in her exercise tolerance. The patient denied any recent cough or fever. She had recently been diagnosed with a *Staphylococcus saprophyticus* urinary tract infection and treated with ciprofloxacin and pyridium for pain. Her presenting symptoms began shortly after taking two doses of the medicines. She described dark urine and yellowing of the eyes. Her father, half-brother and two cousins were diagnosed with Hemoglobin Zurich but were otherwise healthy.

Physical examination was notable for general pallor. Scleral and sublingual icterus were present. Cardiac examination revealed a systolic ejection murmur. The spleen tip was palpable below the costal margin. There were no petechiae.

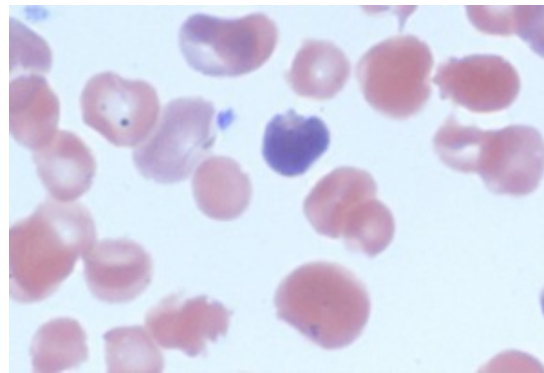
LABORATORY DATA

Basic metabolic panel showed normal blood urea nitrogen and creatinine. Complete blood count showed WBC 18,900/ μ L, hemoglobin 7.5 g/dL, and platelets 257,000/ μ L with reticulocyte count 33% and reticulocyte index of 5. Schistocytes, Bite cells and Heinz bodies were present on peripheral smear. Bilirubin was 9.7

mg/dL with a direct fraction 0.7 mg/dL, serum haptoglobin 3 mg/dL and LDH 495 units/L. Hemoglobin electrophoresis fractionated to 66 % Hgb A, 33% variant hemoglobin, A2 0.3% with Methemoglobin 0 %. Urinalysis was normal. Coombs' test was negative. ANA and Cardiolipin IgG and IgM Antibodies were negative.

IMAGING

Abdominal ultrasound was notable for splenomegaly with the spleen measuring 12.4 cm.



Blister cells and microspherocytes compatible with an unstable hemoglobinopathy

DIFFERENTIAL DIAGNOSIS

Drug-induced hemolytic anemia, toxic hemolytic anemia, immune-mediated hemolytic anemia

DIAGNOSIS

Drug-induced hemolytic anemia

DISCUSSION

Hemoglobin Zurich (HZ) was first described by Frick et al. in 1962 in a Swiss family in which two family members developed life-threatening anemia after antibiotic treatment for urinary tract infections. (1) Of the first three families discovered to be affected by HZ, two were described within Maryland. (2,3) Studies have shown that HZ is inherited in an autosomal dominant fashion in which all affected individuals are heterozygotes.

This unstable hemoglobinopathy consists of an amino acid substitution at position 63 of the beta chain. Arginine is substituted for histidine, causing heme loss leading to secondary globin unwinding with the formation of Heinz bodies. (4) When present, the serum concentration of HZ tends to be 22 to 37 % of the total hemoglobin produced. (1-3) The reduced percentage of HZ in the blood is most likely due to a faster rate of auto-oxidation when compared to normal forms. (5) The life span of a red blood cell with HZ is reduced to 11 to 13 days with persistent elevation in reticulocyte count. (1)

Affected individuals tend to be asymptomatic unless exposed to oxidant drugs such as sulfonamides. When exposed to oxidant drugs, affected individuals frequently develop life-threatening hemolytic anemia with elevated methemoglobin, production of Heinz bodies and decreased red blood cell survival to 2 to 6 days.

Increased carbon monoxide levels are known to protect against hemolytic anemia in HZ. The rate of HZ oxidation is slower as carbon monoxide concentration increases, as with tobacco use. (6) Our patient had quit smoking recently; this may explain why her first episode of hemolytic anemia did not present until she was 21 years old and no longer had the potential protective effects of smoking.

Pyridium is used to treat pain secondary to urinary tract infections. Initially developed in the 1930s, it is now available over the counter. As first reported in 1951, pyridium can cause methemoglobinemia and hemolytic anemia with Heinz bodies. (7-9) No studies have shown the exact mechanism by which pyridium causes Heinz body formation; however, one of its metabolites has been shown to generate superoxide radicals and

hydrogen peroxide. (10) Pyridium-induced anemia is believed to be dose related. (12)

There has been at least one previously reported case of hemolytic anemia in a hemoglobin Zurich positive patient after pyridium use. (11) This case illustrates that commonly prescribed and seemingly innocuous medications may have serious side effects.

Acknowledgement: John Hess, MD, Professor of Pathology and Medicine

REFERENCES

1. Frick PG, Hitzig WH, Betke K. Hemoglobin Zurich. I. A new hemoglobin anomaly associated with acute hemolytic episodes with inclusion bodies after sulfonamide therapy. *Blood* 1962;20:261-71.
2. Rieder RF, Zinkham WH, Holtzman NA. Hemoglobin Zuerich; Clinical, Chemical and Kinetic Studies. *Am J Med* 1965;39:4-20.
3. Dickerman JD, Holtzman NA, Zinkham WH. Hemoglobin Zurich. A third family presenting with hemolytic reactions to sulfonamides. *Am J Med* 1973;55(5):638-42.
4. Bachmann, et al.. Hemoglobin Zurich. II. Physicochemical properties of the abnormal hemoglobin. *Blood* 1962;20:272-86.
5. Di Iorio EE, Winterhalter KH, Mansouri A, Blumberg WE, Peisach J. Studies on the oxidation of hemoglobin Zurich (beta 63 E7 Arg). *European Journal of Biochemistry* 1984;145(3):549-54.
6. Lanir A, Caughey WS, Charache S. Oxidation of carbonyl hemoglobins by ferricyanide. Hemoglobins A, Osler (beta 145 Tyr replaced by Asp) and Zurich (beta 63 His replaced by Arg). *European Journal of Biochemistry* 1982;128(2-3):521-5.
7. Crawford SE, Moon AE, Jr., Panos TC, Hooks CA. Methemoglobinemia associated with pyridium administration; report of a case. *J Am Med Assoc* 1951;146(1):24-5.
8. Gabor EP, Lowenstein L, De Leeuw NK. Hemolytic Anemia Induced by Phenylazo-Diamino-Pyridine (Pyridium). *Can Med Assoc J* 1964;91:756-9.
9. Greenberg MS. Heinz body hemolytic anemia. "Bite cells" - a clue to diagnosis. *Arch Intern Med* 1976;136(2):153-5.
10. Munday R, Fowke EA. Generation of superoxide radical and hydrogen peroxide by 2,3,6-triaminopyridine, a metabolite of the urinary tract analgesic phenazopyridine. *Free Radical Research* 1994;21(2):67-73.
11. Virshup DM, et al. Unique sensitivity of Hb Zurich to oxidative injury by phenazopyridine: reversal of the effects by elevating carboxyhemoglobin levels in vivo and in vitro. *Am J Hematol* 1983;14(4):315-24.
12. Noonan HM, Kimbrell M, Johnson WB, Reuler JB. Phenazopyridine-induced hemolytic anemia. *Urology* 1983;21(6):623-4.

Clinical Vignette: Kappa Light Chain Multiple Myeloma

Issue 1

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Rebecca Powell, MD, PGY-3 in Internal Medicine

PRESENTATION

A 56-year-old man with HIV infection presented with intermittent abdominal pain for two months, increasing in intensity over the previous week. The pain was diffuse and accompanied by nausea and non-bloody vomiting. Intermittent flank pain was present and occasionally associated with hematuria. His last bowel movement was four days prior to presentation. He had no fevers or weight loss. He had presented to the emergency department with similar symptoms in the past two months, and received intravenous fluids and an enema with relief of his symptoms. An unspecified underlying psychiatric diagnosis was noted in his chart. He had not sought routine primary care in over two years. He took no medications.

Physical examination was notable for a soft abdomen without tenderness, rebound or guarding and absence of costovertebral tenderness.

LABORATORY DATA

Initial laboratory data included white blood cell count 4700/ μ L, hemoglobin 10.3 g/dL, platelets 147,000/ μ L with 41% neutrophils, 37% lymphocytes, 15% monocytes, 5% eosinophils and 2% basophils, CD4 333/mm³. Blood glucose, sodium, potassium and bicarbonate levels were normal. Creatinine was 3.4 mg/dL, increased from his baseline 2 years ago of 1.5 mg/dL. Calcium was 19 mg/dL with albumin 4.0 g/dL, total protein 7.9 g/dL and phosphorous 2.9 mg/dL. HIV viral

load was 86,000 copies/mL. PTH was 10 ng/dL and 1-25 dihydroxyvitamin D level 16 pg/mL. Serum and urinary protein electrophoresis and ACE level were normal. Urinalysis showed large blood. Urinary calcium excretion was 93 mg/24hr and urine total protein was 224mg/24hr. Serum free kappa level was 284.1 mg/L and free lambda was 31.1 mg/L with kappa/lambda ratio of 9.1. PTHrP level was normal. C-reactive protein was 0.142 mg/dL, and beta-2-microglobulin was 23.4 mg/dL.

IMAGING

Computerized tomography of the chest, abdomen and pelvis revealed a L2 vertebral body cyst and one enlarged pelvic lymph node. There was no evidence of nephrolithiasis. A whole body bone scan showed mild activity throughout the spine, sternum, ribcage, scapula, pelvis, and proximal femurs. Skeletal survey demonstrated degenerative changes in the spine without lytic lesions or compression fractures.

PATHOLOGY

An axillary lymph node biopsy was performed showing scant small mature lymphocytes. A biopsy of the L3 vertebral body cyst with bone marrow aspiration was completed. The bone marrow was with > 90% cellular with atypical plasma cells and lack of cytoplasmic immunoglobulin staining. It showed surface expression of CD138, CD56, MUM1, and BCL-1 and expressed kappa light chain restriction consistent with plasma cell dyscrasia.

DIAGNOSIS

Hypercalcemia secondary to kappa light chain MM

DISCUSSION

This patient went through an extensive work-up to elucidate the etiology of his hypercalcemia, renal insufficiency and anemia.

A low normal PTH with a normal phosphorus made primary hyperparathyroidism unlikely. Normal 24 hour urine calcium would be doubtful in familial hypocalciuric hypercalcemia. Sarcoidosis would be atypical with a normal ACE level and normal chest imaging. Concern for malignancy associated hypercalcemia was high given his acute presentation. Despite normal SPEP and UPEP and normal PTHrP level, a bone marrow biopsy was performed which ultimately lead to the diagnosis of kappa light chain multiple myeloma.

Plasma cell dyscrasias are a diverse group of diseases characterized by accumulation of plasma cells and/or immunoglobulins. Risk factors include ionizing radiation and industrial chemical exposure. The most common form of dyscrasia is monoclonal gammopathy of unknown significance, a premalignant disorder with a risk of progressing to multiple myeloma or other related disorders. Multiple myeloma includes three uncommon variant presentations: light chain MM, non-secretory MM and plasma cell leukemia.

This case illustrates the rare presentation of light chain only myeloma. Electrophoresis and immunofixation studies are relatively insensitive for the detection of free light chains. The serum free light chain assay is capable of detecting free light chains even when these levels are undetectable by SPEP and IFE. The free light chain assays are best performed on serum rather than urine because of the filtering effects of the kidneys. The serum free light chain assays have greater sensitivity than is available with SPEP, UPEP, and IFE and are automated and require less time to perform than electrophoresis. The use of free serum light chain has helped diagnose

many cases of early AL amyloidosis in the medicine clinics, where it is routinely used as screening for patients with peripheral neuropathy, proteinuria, and infiltrative cardiomyopathy.

Approximately 20% of patients with myeloma present with hypercalcemia at some point in their illness.

Hypercalcemia in myeloma is usually secondary to bone destruction by myelomatous deposits causing a marked increase in osteoclastic bone resorption. (3) Hypercalcemia without lytic lesions as in non-secretory myeloma is likely caused by stimulation of osteoclasts by osteoclast activating factor, a lymphokine that is secreted by malignant plasma cells and that acts on bone broadly, rather than only at the site of myelomatous deposits. (2,4)

This clinical vignette illustrates the persistence necessary to arrive at a diagnosis. The symptoms of abdominal pain, nausea and psychiatric illness were nearly classic for hypercalcemia. Myeloma was not considered initially because the total protein and electrophoresis were normal. A bone marrow biopsy should be considered as part of a hypercalcemia evaluation in addition to complementary initial testing of serum light chain assays with SPEP and UPEP. This patient's renal failure resolved with intravenous fluids. His hypercalcemia responded well to bisphosphonate therapy. He was subsequently treated with bortezomib, cyclophosphamide and dexamethasone chemotherapy. Ritonavir, darunavir, and tenofovir/emtricitabine were initiated for treatment of HIV.

Acknowledgement: Ashraf Badros, MD, Professor of Oncology

REFERENCES:

1. Blade J, Kyle RA. Nonsecretory myeloma, immunoglobulin D myeloma, and plasma cell leukemia. *Hematol Oncol Clin North Am* 1999; 13(6): 1259-72.
2. Chew D and Player JR. Hypercalcemia in a patient with non-secretory myeloma. *Postgraduate Medical Journal* 1988; 64, 438-440.
3. Stewart AF. Hypercalcemia associated with cancer. *NEJM* 2005, 352: 373-379.
4. Mundy, GR, et al. Evidence for the secretion of an osteoclast stimulating factor in myeloma. *NEJM* 1974, 291: 1041-1046.

Clinical Vignette: Thyrotoxic Periodic Paralysis

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Shiven Patel, MD, PGY-3 in Internal Medicine

Jenny Tuan, MD, PGY-3 in Internal Medicine

PRESENTATION

A 17-year old man with a two year history of Graves' disease presented shortly after a fall. He described acute weakness that left him unable to move his lower extremities or stand. He also reported numbness in his legs. He denied fever, headache, dysarthria or dysphagia. During evaluation, he developed acute upper extremity weakness and numbness similar to his lower extremity symptoms. Home medications were methimazole and atenolol.

Vital signs were notable for tachycardia. Proptosis affected the left eye more than the right. Cardiovascular examination revealed tachycardia with regular rhythm and no murmurs, rubs or gallops. Cranial nerves were intact. Muscle strength was 2/5 in both upper and lower extremity proximal muscle groups and 4/5 distally. Reflexes were diminished diffusely. Sensation was intact to light touch and pinprick throughout all extremities.

LABORATORY DATA

Laboratory data included potassium 1.8 mEq/L, thyroid stimulating hormone 0.013 IU/mL, thyroxine 5.3 ng/dL and creatine kinase 84 IU/L. Urine potassium level was 19 mEq/L. Otherwise, complete metabolic panel, complete blood count, and coagulation panel were within normal limits.

IMAGING

Electrocardiogram revealed sinus tachycardia and the presence of U waves. Computed topography of the head was normal.

DIFERENTIAL DIAGNOSIS

Cerebral vascular accident, thyrotoxic periodic paralysis, Guillain Barre syndrome

DIAGNOSIS

Thyrotoxic periodic paralysis

DISCUSSION

Thyrotoxic periodic paralysis (TPP) occurs in 2% of patients with thyrotoxicosis, regardless of etiology. It is seen most commonly in Asian patients and in patients with Graves' disease. Interestingly, TPP is twenty times more common in men despite a higher incidence of thyrotoxicosis in women. TPP occurs most often in the second to fourth decades of life.

The pathophysiology of this disorder centers on the sodium-potassium-adenosine triphosphate (Na/K ATP) pump. Hyperthyroidism creates a hyperadrenergic state which stimulates these receptors. Furthermore, there is evidence that thyroid hormone itself activates these pumps. Insulin is also a known stimulant, which may explain why meals rich in carbohydrates have been described to precipitate episodes of TPP. The overall effect is profound hypokalemia, which renders neuromuscular junctions minimally responsive to nerve impulses and leaves myocytes hyperpolarized. (1)

Classically, the paralysis affects lower more than upper extremity proximal musculature. Distal muscles typically are spared. Paralysis may last anywhere from 3 to 96 hours. Paralysis reversal occurs first in those muscles affected last by paralysis. Most cases do spontaneously resolve. Deep tendon reflexes are often diminished or absent, but ocular, bulbar, and respiratory muscles as well as sensation and consciousness tend to be spared. Arrhythmias can be potentially life threatening. (2)

Diagnosis requires hypokalemia in a setting of abnormally high thyroid function tests with the aforementioned clinical findings. Urinary potassium is often low (<20 mmol/L). It is important to note that while hypokalemia may be seen on laboratory studies, total body potassium may be normal. Therefore, potassium should not be repleted too aggressively. This will help prevent rebound hyperkalemia. Some propose that nonselective beta-blockers such as propranolol should be the mainstay of treatment, as they serve both to inhibit the Na/K ATPase pump and reduce tachycardia with minimal risk for rebound hyperkalemia. Definitive treatment targets the underlying hyperthyroidism, usually by radioactive iodine or thyroidectomy. Radioactive iodine may worsen Graves' ophthalmopathy and therefore is contraindicated in patients with this condition. Once patients are permanently euthyroid, there is complete remission of TPP. (3)

This patient admitted poor adherence to methimazole secondary to pruritus. Propylthiouracil was initiated and atenolol was increased. Appropriate potassium repletion was achieved. Within 24 hours, the patient experienced complete resolution of symptoms. A total thyroidectomy was performed three weeks after initial presentation.

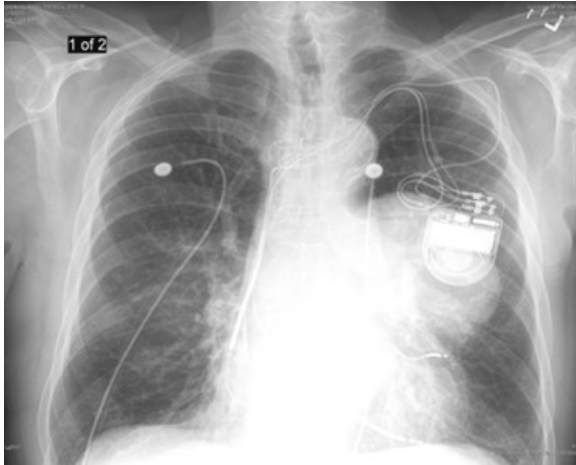
REFERENCES

1. Lam L, Nair RJ, Tingle L. Thyrotoxic periodic paralysis. *Proc (Bayl Univ Med Cent)* 2006, 19:126-129.
2. Lin, SH. Thyrotoxic periodic paralysis. *Mayo Clin Proc* 2005, 80(1):99-105.
3. Pothiwala, PS, Levine, SN. Thyrotoxic periodic paralysis: a review. *J Intensive Care Med* 2010, 25:71-77.

Image Challenge.... We Dare You!

Issue 1

May 2011



WHAT IS THE DIAGNOSIS?

Left Atrial Enlargement

Large Hiatal Hernia

Sphenous Vein Aneurysm

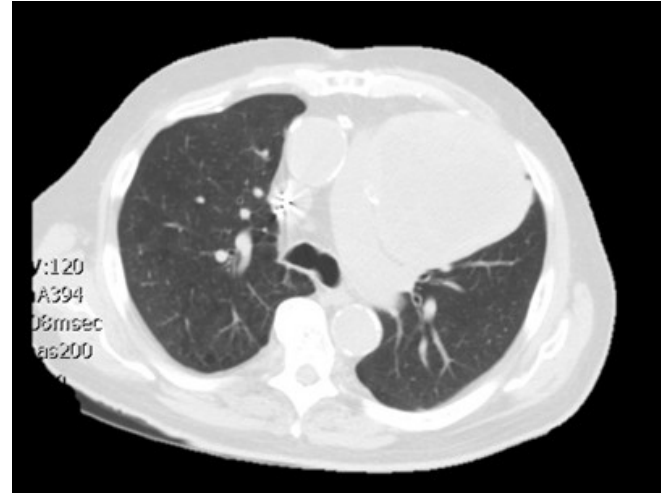
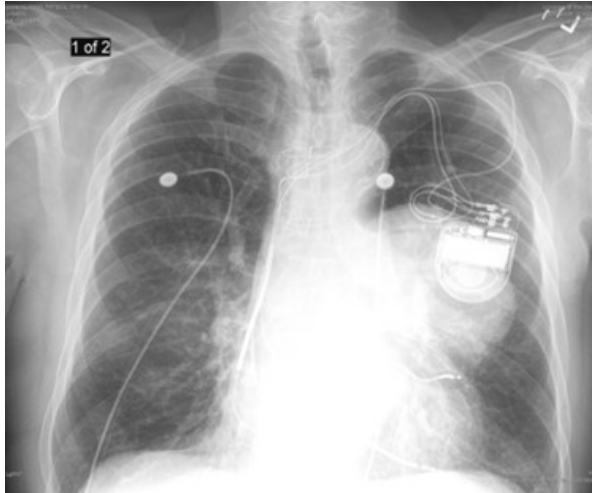
Bronchogenic Carcinoma

Aspergilloma



Answer on the next page....

Image Challenge: Saphenous Vein Aneurysm



A 73-year old man with coronary artery disease status post coronary artery bypass graft presented with chest tightness and dyspnea. Chest radiography demonstrated an anterior mediastinal mass projecting over the left hilum, measuring 13.6 cm by 12 cm. Computed tomography of the thorax demonstrated a large heterogeneous mass that was inseparable from one of the bypass grafts, likely representing a large saphenous vein aneurysm. The patient experienced ventricular tachycardia cardiac arrest and did not survive. Saphenous vein grafts typically begin to deteriorate after 5 to 7 years. Only 50% of saphenous vein grafts remain patent after 15 years. (1) Case series suggest that the incidence of saphenous vein aneurysms is < 1%. (2)

Acknowledgement: Robert E. Hood, MD, Assistant Professor of Medicine

REFERENCES

1. Loop FD et al. Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events. *NEJM* 1986; 314(1):1.
2. Nishimura et al. Saphenous vein graft aneurysm after coronary artery bypass grafting. *Ann Thorac Cardio Vasc Surg* 2009; 15(1): 61-63.

Viewpoint: Restricted Work Hours

Facing New Challenges in Medical Training

Issue 1

May 2011

Esteban Gallego, MD, PGY-3 in Internal Medicine

At 2 o'clock on a Saturday morning, I was in the emergency room interviewing the fourth admission of the night. She was an elderly woman being admitted for pneumonia, and she did not yet know that she had radiologic findings concerning for malignancy. Her daughter was quite animated, asking questions about me and sharing details about her own life. As we neared the end of the interview, she asked, "So will I be seeing you in the morning?" Politely, I responded that she would not and pointed out that the intern would be her primary caregiver. As I left the room, it occurred to me that I would likely never see her again.

This is becoming a common scenario in the age of duty hour restrictions. My responsibilities that night were extensive and included three other admissions, some of them quite complex. However, my duties ended once the regular team arrived the following morning. I quickly and succinctly told my colleagues about their new patients, handed off the notes, and offered a list of tasks to complete. In those ten minutes, I tried to summarize the facts I had learned while reading through medical records, the information I had gathered from talking with the patients, and even the nuances that only I had observed on my exams. My role that night was simple. I covered admissions and consults while the call resident went home to rest. Eliminating the overnight call left a gap in coverage, and my job was to fill that gap. Once the morning came, my job was done.

We are now on the eve of a major change in medical

training. Interns will no longer take 30 hour calls. Their overnight time in the hospital, those critical lonely hours when we become doctors, will be limited. The change in staffing may leave gaps in coverage throughout the hospital and throughout the day. These gaps will be filled increasingly through isolated shifts covered by colleagues. Much like my experience that Saturday morning, we will admit more patients whom we will never see again and care for more patients whom we will know peripherally.

The reaction from some colleagues has been negative. The changes were made to limit resident fatigue and improve patient safety. Furthermore, it may seem appealing not to work 30 hours without rest. Yet many residents anticipate more hand-offs and gaps in care that will negatively impact patients. The need to cover shorter shifts more often is forcing us to stretch the workforce. Perhaps their reaction is a testament to how hard-working residents are and their commitment to good patient care.

On the other hand, I have seen the negative impacts of fatigue over the course of my residency. At the very least, I know that in my 25th hour of sleepless work, I am more likely to miss lab abnormalities or enter orders incorrectly. At its worst, I worry that intelligent, conscientious, competent residents who have been at work too long would miss life-threatening diagnoses. When I cover isolated night shifts, I notice that my attitude is much more positive. Rather than rolling my eyes when the pager goes off or deferring work so that I can squeeze in a nap, I have more energy to see my

patients and do appropriate work-ups. I am much more willing to make the extra phone calls, talk with relatives, reevaluate patients, and take any extra steps to make patient care great, not just satisfactory.

This is not the first huge change in medical training. My generation of colleagues and I have not worked over 100 hours weekly on a regular basis or spent every other night in the hospital. Surely, the first wave of duty hour reform marked a dramatic change. However, medical training continued on and we still have excellent physicians who graduate every year. The change that comes along now will be no different.

The challenges we face, however large, are not insurmountable. They will be met at both institutional and individual levels. The changes will require us to take initiative in our training. For example, hand-offs should be treated with much greater importance. Rather than talking about patients in ten minutes, why not see a sick patient together to establish continuity? We will need to shift our attitude such that patients do not “belong” to anyone else. For those 12 hours, cross-cover patients are “our” patients and their medical care should be prioritized as such. Lack of follow-up with patients is another gap in our training as we limit call hours. Why shouldn’t I find time to visit patients whom I admitted a few nights ago and look through their charts to learn about their hospital course? Why shouldn’t I approach my colleagues and friends for feedback on the decisions I made at night? We also must view hand-offs from the patient’s perspective. I had established a rapport with my patient’s daughter, but in the morning she would see a brand new group of people. In fact, she could see six different faces each time she asked to speak with a physician that weekend. If she saw me once or twice more, would that make her feel more comfortable with her mother’s care? We can acknowledge to our patients that the medical team caring for them consists of many people, but that we are committed as a team to strong communication with each other and prioritizing the patient’s wellbeing

above all.

The change in medical training is happening and with it will come a number of unintended consequences. We must all face the challenge of preserving the key portions of our medical training. We will have to find new ways to ensure continuity in our patient care, to ensure that we learn from the actions that we take, and to minimize lapses in care as we cycle through our shifts. While institutions may address some of these points, individual residents will continue to bear the responsibility of ensuring good care for their patients and good training for themselves.

Expressions: Trust

Issue 1

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Laila Tabatabai, MD, Internal Medicine Resident PGY-2

I've often wondered how it would feel to come face-to-face with a former patient outside the hospital. To see them in clothes that button and zip up, rather than flimsy hospital gowns that leave all too little to the imagination. To hear them laugh, curse, or simply speak freely. To meet them on a level playing field.

I no longer have to wonder. I met a former patient of mine in Whole Foods last week. We were in the Pasta, Beans, Nuts & Legumes aisle, which inexplicably housed biscotti and coffee as well. I reached for a bag of chocolate-dipped macadamia nuts, thought better of it, and chose the Marcona almonds instead. He seemed overwhelmed by the eleven varieties of whole-grain pasta available in various shapes and sizes.

Our eyes met – I saw a flash of recognition in his, and then something else. Fear, perhaps? Anger, maybe. Or was it repulsion?

Did I remind him of a darker time in his life, a time he wished to bury beneath happier memories? Did I represent restrictions and rules which he would rather forget?

I walked quickly down the aisle, forgetting to buy the pine nuts for pesto and the farfalle.

I couldn't remember his name. I remembered his story, though. He had come in with chest pain. He'd ignored it for weeks, trying to dull it with antacids and NSAIDs. That was before it made him dizzy, diaphoretic, and brought him to his knees. His wife had called the paramedics.

I saw him the morning after his catheterization showed blockages in all major arteries. Reviewing the cath films took over 20 minutes on rounds; our post-call intern was almost in REM and I had to stifle several

yawns before the gory details were laid bare. When it came to the plan, our attending was succinct: our patient needed a CABG.

"You're awfully young to be my doctor, aren't you?" It was meant as a joke, but I sensed snarky undertones in his voice that irked me.

And you're awfully young to have triple-vessel disease, aren't you? I bit my tongue, smiled, and explained that I was a first-year physician.

He spent several more days on our service in preparation for cardiac surgery. With each test and procedure, he became a little less sure of himself. He asked more questions and listened carefully to my answers. After meeting the CT surgeon, the reality set in.

"I'm going to make it, aren't I?" His voice was plaintive.

I faced him and his wife. I focused on their hands, tightly clasped together. Her knuckles were white. I saw their wedding bands, matching in platinum.

I took a deep breath.

"Of course you will."

And he did. Here he was, over a year later. He looked thinner, but well. It was bizarre to see him standing there. He was like an apparition. A figment of my imagination. A mere moment in the blur of intern year. He had been a room number, an MRN, a discharge summary dictated by phone.

But here he stood, ahead of me in the checkout line. I was struck by how I felt – grateful. There are some happy endings, I guess. I wish I'd known this all along.

He caught my eye again before leaving. This time, I saw him smile.

Expressions: A Reflection on Malawi

Issue 1

May 2011

Clare Lee, MD, PGY-3 in Internal Medicine

If you had asked me last year where Malawi is located, I would have had no clue. Now that I recently returned from an away rotation at St. Gabriel's hospital in Malawi, Africa, I can definitely share a story or two on Malawi in addition to telling you where it is on the map. The initial glimpse of Malawi as our airplane landed gave me goose bumps as I stared at its lush green vegetation and gentle yet majestic mountains. I started to doubt whether I had brought enough things to sustain me in this foreign land for the next three weeks. It didn't help that I picked up the Malawi travel book about half an hour prior to landing and started reading about all women in Malawi wearing skirts (I did not bring any skirts) and about Tumbu flies that lay eggs on drying laundry which can later bury into human skin. As I departed the modern heaven in airplane form, I was greeted by an unusually fresh breeze, warm temperatures and the brightest smiles from people that made the New Yorker in me a bit nervous.

A driver dispatched from St. Gabriel's hospital held a big sign in his hands with my name on it. With much relief, I introduced myself and boarded the old Jeep. The driver seemed comfortable in his long-sleeve shirt and corduroy pants, but I started sweating in my T-shirt and thin cargo pants. I distracted myself from the heat inside the car by paying attention to the view out the



window of mostly unfamiliar plants and trees, as well as numerous pedestrians and bikers along the sides of the paved road. Indeed, all women on the roads wore long skirts made of chitenje, or traditional fabric with colorful and beautiful patterns on it. Bikers often carried impossibly large loads in front of and behind themselves while pedestrians seemed to have the extraordinary gift of balancing all their goods on top of their heads. The road we traveled seemed to be the only road in town. Its path was mostly straight with no side roads or intersections for a good while. The Malawi people walking and biking unhurriedly to their destinations, unfazed by the sun's unrelenting heat, seemed so different from the occasional joggers or bikers on the sides of roads back home.

After an hour-long ride from the airport, we arrived at Zitha House in Namitete, guest housing for visiting volunteers located near the hospital. I was assigned a

room with a single bed, large window and private bathroom complete with a stand-up shower. This all seemed too good to be true, especially considering I was visiting the fourth poorest country in the world with a gross national income per capita of \$690. My expectations had been modest. Soon after my arrival, I was greeted by

fellow visiting doctors who were returning home from the hospital. I had the good fortune of arriving at Zitha House when it was nearly filled to capacity with 11

people. Almost half of them were visiting from Canada while the rest were from the States. We had one IT person working on incorporating text message technology into outpatient care follow up. The rest were doctors of pediatrics, family medicine and internal medicine with one nurse. I quickly learned that living with these colleagues was one of the highlights of my trip. They were all so well-traveled with interesting backgrounds and experiences. Whenever the electricity went out in the house (daily surprises that made our portable headlamps and flash lights indispensable) or the insects on the kitchen counter diminished our appetites, Nurse Sam would tell stories from her recent Congo project that rendered all our complaints insignificant.

Despite the long trip to Malawi, I was all too excited and eager to start my first day of work the next day. St. Gabriel's Hospital was founded 50 years ago by sisters from Luxembourg and since grew to a 160-bed hospital. It is a beautiful one-story red brick building with ample sunshine shining through its many windows. The building consists of one floor with many different wings housing a male ward, female ward, pediatric ward, outpatient wing, palliative wing, obstetrics and gynecology facilities, a surgical theater and a private wing. A typical work day at St. Gabriel's hospital starts off with morning report, in which the staff discusses overnight admissions and the current census and status of critically ill patients. After morning report, I joined one of the medical officers (equivalent to interns in the States) to spend the morning at a busy outpatient clinic where patients and guardians crowd the hallway waiting to be seen. The primary chief complaint was "malungo" in Chichewa which means fever, as well as malaria. The entire encounter took place over a few minutes, during which time the medical officer and I took a brief history, performed a focused exam and made decisions whether to treat as an outpatient or to admit. As one patient exited the exam room, the next patient walked in even before the door could close. The time was spent seeing as many patients as possible. By the end of the morning,



traffic in the hallway had barely diminished but it was time to head to the inpatient ward.

Adult inpatients were placed separately by gender. I worked mostly in the female ward seeing 20 to 30 patients a day, many of whom were new admissions seen previously by nurses or medical officers at outpatient offices. Aside from the language barrier (I relied on translation help by the nurse or medical officer) and the overwhelming volume of patients and patient turnover, the real challenge for me was in utilizing limited laboratory and imaging resources to serve the patients appropriately. At St. Gabriel's, the laboratory processes blood counts, liver panels, blood smears, sputum smears and body fluid analysis. Imaging capacity includes chest and abdominal X-ray and portable ultrasound. The list of medications available at St. Gabriel's fits onto one double-sided sheet of paper. Supplies are often in reusable forms such as stainless steel containers, tools, and glass bottles. Sterile gloves and local anesthetics are used for surgical procedures, not necessarily for bedside procedures such as lumbar punctures or thoracenteses. Given such limitations, I had to fight the urge to defer diagnosis until further testing/imaging/consult results were available, as was often the case back at home. I had to learn to trust the power of the history and physical exam.

Several other unique challenges included understanding the cultural context of our patients, eliciting pain histories from people who normally do not complain of pain, and learning the limits of medical care at the hospital and in Malawi. A young woman with severe pneumonia, labored breathing and pulse oxygenation below 85% refused supplemental oxygen because she felt the disease was a sign of God's curse on her. On daily rounds, we asked another lady admitted with gastroenteritis if she could tolerate food intake. In retrospect, I realized she had no access to food as an inpatient since the hospital provides meals only to those admitted with severe malnutrition. I learned the small black lines on patients' bodies which I assumed to be tattoos were actually marks left by the local witch doctors.

Patients often came to St. Gabriel's as their last resource after exhausting all local medicine options. A 33 year old woman with metastatic breast cancer complained of difficulty walking and was found to have a complete left femur fracture and multiple hairline pelvic fractures. She did not complain of much pain. She subsequently was transferred to the palliative care unit, the only place in the hospital where IV morphine was available. Diagnosing terminal cancer and seeing children struck with Kwashiorkor or other diseases of severe malnutrition filled me with discomfort and sorrow.

Outside the hospital door, Namitete village is full of life. Streets are full of kids of all ages playing outside alongside goats, chickens and cows. The weather could not be better, with balmy 80 degree temperatures and intense African sun mixed with brief, daily downpours. Above all, caring for the patients of St. Gabriel's hospital was the best part of the trip. Despite the challenging circumstances, I welcomed the chance to rely on bedside physical exam skills and medical knowledge to care for patients who were all too grateful. Despite the occasionally stifling sensation of being unable to order labs and imaging that I am so accustomed to back home, it felt liberating to practice medicine in its purest form. There was little in between the physician and the patient. It also gave me the opportunity to grow as a person by witnessing poverty and the lively strength and peace embraced by the people of Malawi despite this inequity. On my way back home, my suitcase was filled not only with beautiful ebony wood carvings but with fond memories of the wonderful people and nature of Malawi.



Images in Medicine: Serum Sickness

Issue 1

May 2011

Michael Allison, MD, PGY-2 in Internal Medicine and Emergency Medicine



A 56-year old woman presented with a palmar skin rash. She had aplastic anemia and had been treated for six days with horse anti-thymocyte globulin (ATG) and cyclosporine. Physical examination was notable for erythematous plaques and purpura on the palmar surfaces of both hands.

Serum sickness is an immune complex deposition disorder resulting from the interaction between host antibodies and circulating foreign antigens. The insoluble Ag:Ab complexes precipitate in the skin, joints and internal organs leading to an acute inflammatory response. It is a well-described phenomenon that occurs in up to 86% of patients treated with horse ATG in one seminal case series. It is also associated with other immunosuppressive medications and antibiotics. Symptoms usually begin 7 to 14 days after initiating therapy. What begins as erythema and purpura of the lateral fingers, palms, and soles can progress to a morbilliform eruption, flu-like symptoms with gastrointestinal distress, and arthralgias or arthritis. Treatment includes steroids and the use of antihistamines for symptomatic relief. This patient received a two-week taper of steroids with complete resolution of her palmar rash.

Acknowledgement: Ivana Gojo, MD, Associate Professor of Medicine

REFERENCE

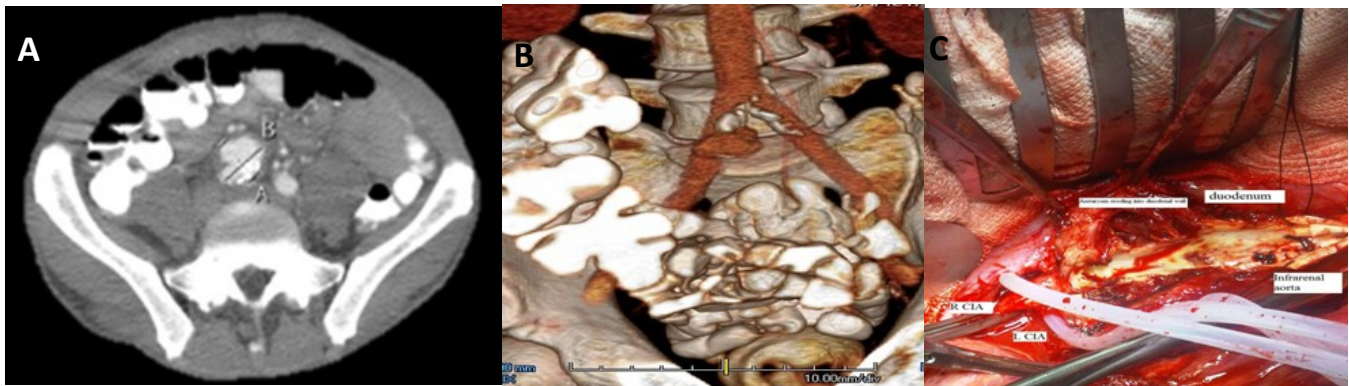
Bielory L, Gascon P, Lawley TJ, Young NS, Frank MM. Human serum sickness: a prospective analysis of 35 patients treated with equine anti-thymocyte globulin for bone marrow failure. *Medicine* (Baltimore)1988 ;67(1):40-57.

Images in Medicine: Mycotic Pseudoaneurysm

Issue 1

May 2011

Lauren Hawkins, MD, PGY-1 in Internal Medicine



A 50-year old man presented with acute right lower quadrant abdominal pain. He had a history of acquired immune deficiency syndrome (AIDS) (CD4+ 12 cells/ μ L) and hepatitis C infection. His temperature was 38.1 $^{\circ}$ C. Palpation of the right lower quadrant was benign without guarding or rebound. No masses were palpated. Blood cultures were positive for *Salmonella enterica* serotype Enteritidis. Contrast-enhanced computed tomography of the abdomen and pelvis demonstrated a 2.5 x 2.86 cm pseudoaneurysm in the right common iliac artery (Panel A, axial image; Panel B, three-dimensional coronal reconstruction), with an irregular lobular contour. Anti-retroviral therapy and antibiotics were initiated. Worsening abdominal pain with subsequent aneurysmal enlargement seen on repeat computed tomography prompted urgent surgery. The patient underwent pseudoaneurysm excision (Panel C), arterial graft placement and left axillary arterial bypass. Pathology of the excised tissue was consistent with pseudoaneurysm. Mycotic aneurysm or pseudoaneurysm can occur secondary to bacteremic seeding of an existing intimal injury, septic emboli to the vasa vasorum, a continuous infection extending into the vessel wall or direct inoculation. It is often associated with *Salmonella* bacteremia, which is more common in patients with human immunodeficiency virus (HIV), but reports of pseudoaneurysms requiring surgical intervention in HIV-infected patients are rare.

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REFERENCE

Lopes RL et al. Infectious thoracic aortitis: a literature review. *Clin Cardiol.* 2009; 32(9):488-90.

*In Review:**Treatment Considerations in Chronic Hepatitis C*

Issue 1

May 2011

Arul Thomas, MD, PGY-3 in Internal Medicine

The hepatitis C virus (HCV) has infected nearly four million Americans. (1) Global infection is estimated to be 175 million persons. (1) The virus causes significant morbidity and mortality, though often in a slow manner that can encompass liver cirrhosis, end stage liver disease, hepatocellular carcinoma (HCC) and death. While many primary prevention practices, such as blood product screening, have reduced the incidence of hepatitis C in the United States, there remains a large pool of chronically infected hepatitis C patients. Unfortunately, the majority of Americans infected are undiagnosed with only one half of those infected and diagnosed having been treated with interferon therapy—a therapy that can potentially eliminate the virus from the blood stream (2). The treatment of chronic hepatitis C is not perfect or ideally optimized for every patient, but it can be successful. Clinical judgment and circumstances dictate treatment for high risk groups seen commonly in urban practice, such as those coinfecting with human immunodeficiency virus (HIV). The likelihood of achieving sustained virologic response (SVR) at six months or more after cessation of treatment is affected by viral and host factors. Gene expression research will predict treatment outcomes and customize therapy in the years ahead.

PRINCIPLES OF TREATMENT

The standard of care treatment for chronic hepatitis C infection is polyethylene glycol interferon (PEG-IFN) combined with the guanosine analogue, ribavirin. Treatment candidates are those with progressive disease, not early or inactive disease. Patients with decompensated cirrhosis are not candidates for PEG-IFN therapy. Interferon treatment can worsen underlying psychiatric disease; as such, patients with

severe, uncontrolled psychiatric disorders are also not candidates for treatment. PEG-IFN may lead to leucopenia and thrombocytopenia, further excluding more patients. Moreover, ribavirin can cause hemolytic anemia, cerebrovascular disease and renal failure.

Elevation in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels is not required for treatment. Identification of the specific virus genotype will help predict treatment response. Sadly, many Americans are infected with genotype 1, which yields a SVR less than or equal to 40 to 50%. Genotype 2 has a much more positive treatment outcome, with over 80% of patients achieving SVR. (2) Patients with genotype 1 require 48 weeks of treatment (compared to 24 weeks for genotypes 2 and 3) and the highest dose of ribavirin. (3) Histologic grade and stage, determined by liver biopsy, quantify the degree of progression of viral infection and are the most important pretreatment clinical variables. (3) Patients with bridging fibrosis and cirrhosis (METAVIR score > 2, Ishak fibrosis score > 3) have the highest likelihood of progressive fibrosis and are the best candidates for treatment. It is controversial whether patients with genotypes 2 or 3 require liver biopsy prior to initiating treatment. Measurement of HCV ribonucleic acid (RNA) levels via polymerase chain reaction has shown that patients with very high levels of HCV RNA respond less well to treatment. (3)

PEG-IFN is available in two forms. One form, PEG-IFN alfa 2a, has a half-life of 80 hours, a weight of 40 kilodaltons, and a fixed dose. The other form is PEG-IFN alfa 2b, with a half-life of 40 hours, a weight of 12 kilodaltons, and weight-based dosing. Interferon binds to cell surface receptors, leading to transcription of genes that mediate antiviral, antiproliferative and immunomodulatory effects. Pegylation of the interferon molecule increases half-life by reducing

degradation and clearance, allowing once-weekly dosing. Ribavirin is dosed between 800 mg (low) and 1200 mg (high). The mechanism of action of ribavirin is disputed, with both an immunomodulatory effect (via Th1 response initiation and molecular level changes) and direct antiviral effects, (3) It works synergistically with interferon. Interferon is administered subcutaneously once weekly, and ribavirin is an oral medication taken daily. Treatment doses are shown in Table 1. Large clinical trials have shown overall SVR of 54 to 56%, with either PEG-IFN alfa 2a or 2b and ribavirin. Genotype 1 SVR exceeded 40%, and genotype 2 and 3 SVR were 76 to 82%. (4,5) For genotype 1 patients, Hadziyannis et al. demonstrated in a randomized, double blind trial that 48 weeks of PEG-IFN alfa 2a with standard dose ribavirin was superior to 24 weeks of therapy. The absolute difference in SVR between 48 and 24 weeks of treatment was 11.2% (95% confidence interval (CI), 3.6% to 18.9%). (6)

McHutchison et al. led a multicenter, randomized controlled study that compared three regimens of treatment to determine which regimen achieved the highest SVR. The first two treatment arms used PEG-IFN alfa 2b, dividing patients into a standard dose interferon group and a low dose interferon group, all of whom received ribavirin. The third treatment arm involved a fixed dose of PEG-IFN alfa 2a with ribavirin. The study enrolled 3070 patients and followed HCV RNA levels for 48 weeks. Ribavirin dosing varied per treatment group, which did not allow a direct comparison of interferon doses and types. Rather, the three groups could only be compared to each other. Nonetheless, SVR did not vary significantly between the two PEG-IFN types (between 38 and 40%). (7) The estimated difference in response rates between standard dose and low dose PEG-IFN alfa 2b was 1.8% (95% CI, -2.3 to 6.0). The estimated difference in response rates between standard dose PEG-IFN alfa 2b and alfa 2a was 1.1% (95% CI, -5.3 to 3.0). Viral response at week 4 correlated

well with achievement of SVR. At week 4, nearly 86% of patients with undetectable HCV RNA had SVR after treatment. This refined the definition of early virologic response (EVR), which traditionally was a greater than or equal to 2 log₁₀ reduction in HCV RNA levels in the first 12 weeks. Data now supported a strong likelihood of achieving SVR if RNA levels decreased in the first 4 weeks.

The principal side effects of interferon therapy are flu-like symptoms, marrow suppression (primarily leucopenia and thrombocytopenia), emotional effects, mood disorder, and autoimmune conditions such as autoimmune thyroiditis. Systemic flu-like symptoms respond well to supportive care. Antidepressants and sleep inducing medications may help with mood and insomnia. It is important to note that depression is the

most common reason for discontinuing therapy. Neutropenia can occur, but with a low risk of infection. (2) Granulocyte-colony stimulating factor is rarely needed. (2) Ribavirin, a teratogenic drug that is excreted renally, may lead to hemolytic anemia as

well as myriad other conditions including sinusitis and gout. Ribavirin doses may be reduced in cases of drug-induced anemia. Erythropoietin injections may also help diminish the severity of anemia. Patient support during treatment is critical to ensure compliance and maximize the likelihood of achieving SVR. (2)

Table 1. Current treatment regimens for chronic HCV infection.²

Genotype	Agent	Ribavirin Dose (mg/day)	Duration
1	PEG-IFN	1000-1200	48 weeks
4	PEG-IFN	1000-1200	48 weeks
2	PEG-IFN	800	24 weeks
3	PEG-IFN	800	24 weeks

BENEFITS OF TREATMENT

Treatment with interferon has been shown to reduce fibrosis predominantly in patients who achieve SVR. Camma et al. studied nearly 1000 patients pooled from three previous trials. (8) Patients were treated with either pegylated or conventional interferon without ribavirin. Histologic grading of liver biopsy samples pre- and posttreatment was analyzed. Approximately half of the patients were genotype 1. Slightly over half of the patients with SVR showed improvement in

histologic grading. A subset of patients with cirrhosis (n=198) showed 34% reduction in fibrosis stage with treatment with either pegylated or conventional interferon. No patient showed complete resolution of cirrhosis.

Clinical outcomes also improve with treatment. Veldt et al. analyzed 479 European and Canadian patients in a retrospective cohort study. (9) These patients were treated with interferon monotherapy from 1990 to 2003. End points of death, liver failure and HCC were evaluated among those with SVR and those who did not respond. Liver failure was specifically defined as ascites, bleeding esophageal varices, jaundice, or hepatic encephalopathy. Those with SVR demonstrated the lowest occurrence of any clinical end point. However, a statistically significant difference between patients with SVR and non-responders was found only in the end point of liver failure. There was no statistically significant difference in the development of HCC between those with SVR and those who did not respond to treatment. The study was limited by retrospectively including patients who were not treated with the same regimens and who were not all treatment-naïve.

Shiffman et al. used data from the large, prospective HALT-C trial to study if the amount of viral suppression from treatment affected clinical outcomes. (10) The main HALT-C trial selected patients with bridging fibrosis or cirrhosis and treated them with low dose PEG-IFN alfa 2a for 3.5 years. All patients previously had not responded to treatment. Patients were retreated with PEG-IFN and ribavirin as a lead-in (n=764, mostly genotype 1). At week 20, if HCV RNA was still detected, patients were assigned to receive low dose PEG-IFN for 3.5 years or placebo. Clinical end points were: specific increase in Childs score, ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, HCC, death or increased fibrosis. Patients with the greatest decrease in HCV RNA prior to week 20 ($> 4 \log_{10}$) had the fewest clinical end points ($p=0.003$). This benefit extended over the course of the study regardless if the patients received maintenance low dose interferon or placebo. Over half of these patients who initially responded strongly could not maintain viral suppression with low dose PEG-IFN. Interestingly, patients who received placebo showed a rapid return to pretreatment HCV RNA levels regardless of viral response during the first 20 weeks.

The study discounted the role of low dose maintenance therapy in preventing negative clinical outcomes. It validated early, large viral suppression as the best predictor of positive outcome and SVR.

HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND HEPATITIS C COINFECTION

Patients with HIV coinfection are common in urban practice. The prevalence of such coinfection varies with the route of exposure for HCV. It may vary from 10 to 14% among those who contracted HCV from high risk sexual exposure, to 85 to 90% among those infected via intravenous drug use. (11) HIV coinfection decreases clearance of HCV after acute infection. It also leads to more rapid progression of liver disease. (11) The Data Collection on Adverse Effects of Anti HIV Drugs (D:A:D) cohort trial studied 23,341 HIV patients. The second leading cause of death in this study was liver disease, second only to acquired immune deficiency syndrome (AIDS). In a newly diagnosed HIV patient, the decision of which virus to treat first is a controversial one. Antiretroviral therapy (ART) can further worsen liver disease, particularly by causing hepatic steatosis. (12) Investigators have found that metabolic syndrome and insulin resistance are associated with hepatic steatosis in HIV/HCV coinfection. (12) This effect may be separate from the known increase in insulin resistance caused by certain protease inhibitors and nucleoside reverse transcriptase inhibitors. In general, it is recommended that patients pursue HCV treatment before ART if they have genotypes 2 or 3, high CD4 counts, acute HCV, or cryoglobulinemia. The remainder of patients, most of whom will resemble those encountered in urban practice, should have ART therapy initiated prior to HCV therapy. (13)

HEPATITIS B VIRUS (HBV) AND HEPATITIS C COINFECTION

Coinfection of HBV and HCV is seen in American urban areas, yet is most studied in Asia where HBV has a higher prevalence. There are case descriptions of superimposed HCV on chronic HBV, as well as occult HBV with HCV infection. In the latter, patients have undetectable HB surface antigen and positive levels of HBV DNA. It is unclear whether coinfection worsens

liver disease. There is also debate regarding whether one virus can suppress replication and activity of the other. (14) It is important in coinfecting patients to determine the dominant virus through serological and virological testing. Liu et al. showed in a Taiwanese study that high SVR could be achieved in coinfecting patients using PEG-IFN alfa 2a and ribavirin. (15) The study included 161 patients with chronic HCV and chronic HBV (documented HB "e" antigen negative) and 160 patients with HCV mono-infection only. Depending on genotype, patients received either 24 weeks (genotype 2 or 3) or 48 weeks of therapy (genotype 1). Overall, 72% of genotype 1 patients coinfecting with HBV achieved SVR, compared to 77% of genotype 1 mono-infected HCV patients. The high SVR rates are in accordance with other values obtained in studies of treatment effect in Asian populations. Of 68 coinfecting patients with detectable pretreatment HBV (although with low viral levels), 49 patients had undetectable HBV at the end of treatment. This includes both genotype 1 and nongenotype 1 patients. At the end of followup, 38 of the 68 patients remained with undetectable HBV. In 77 patients with no detectable HBV pretreatment, 28 had reappearance of HBV. Patients who achieved HCV SVR and those that did not achieve HCV SVR were not significantly different for those patients with HBV reappearance ($p=0.95$). The clear treatment strategy favors those with chronic HCV and low levels of HBV, as tested in this study. For those with highly active, dual virus coinfection, there is not sufficient data to recommend which virus to treat first.

LIVER TRANSPLANT AND HCV

HCV is the main indication for liver transplant in the United States. (2) Clinicians have identified two critical treatment periods affecting HCV patients awaiting transplant. One is pre-transplant, where the goal is to prevent reinfection after receiving a new liver. The second is post-transplant, where the purpose is to eliminate recurrent infection and prevent graft loss (16). Gallegos-Orozco et al. studied liver biopsies of nearly 1000 patients who were transplanted for HCV and found post-transplant HCV recurrence of 49%. (17) Significant HCV recurrence was quantified by evaluating fibrosis and inflammation scores in biopsy samples. It is known that HCV RNA levels decline in

the immediate period post-transplant. Data from pooled studies show disappointing SVR, ranging from 8 to 39% in genotype 1 patients. (16) Similar results are found in patients with recurrent disease treated farther out from transplant. In genotype 1 patients treated prior to transplant, SVR was as low as 13%. (18) Both pre- and post-transplant patients were affected by dose reductions and treatment discontinuation due to adverse effects. A rare condition in some treated patients post-transplant is autoimmune-like hepatitis. This presents with an increase in AST and ALT levels during or after antiviral therapy in patients with a viral response. It appears to be a plasma cell-predominant, portal-based infiltrate with interface hepatitis. Association with autoimmune markers is sometimes present. In some cases, the condition responds to increased immunosuppression. (16)

VARIABLES AFFECTING TREATMENT RESPONSE

The factors associated with SVR can be divided into viral factors and host factors. McHutchison et al. described viral factors as HCV genotype and HCV viral load. (7) The rate and degree of decline in HCV RNA correlates well with the likelihood of achieving SVR. Host factors include African American (AA) race, Latino ethnicity, liver fibrosis stage, age, insulin resistance, immunodeficiency and genetic variation. (7) Many of the host factors can be explored through gene expression studies obtained from liver biopsy samples. Data on race, insulin resistance and genetic variation with regard to interferon signaling have provided fascinating insight into why some patients respond better to treatment than others.

Conjeevaram et al. have shown through the Viral Resistance to Antiviral Therapy to Chronic Hepatitis C (VIRAHEP-C) study that AA patients clearly respond less well than Caucasian Americans (CA) to treatment. (19) The study was a multicenter, prospective analysis that was powered adequately to detect a difference between racial groups. All patients were genotype 1, with 196 AA patients and 205 CA patients. All received PEG-IFN alfa 2a with ribavirin for 48 weeks. The AA patients were heavier and more likely to have a history of hypertension and diabetes mellitus. SVR was achieved in 28% of AA patients, versus 52% of CA patients. The differences were seen as early as four weeks into treatment and persisted throughout the

treatment period. Relapse rates post treatment were comparable (32% for AA, 25% for CA, p=0.30). Adverse events were also similar between the racial groups. Interestingly, EVR (defined at week 12) was less common in AA, at 61% compared to 78% for CA (p=0.003). The negative predictive value of this was similar between the races (97% for AA, 100% for CA), yet the positive predictive value was significantly different (43% for AA, 67% for CA, p< 0.001). It can be inferred that early response in AA patients does not correlate as well with SVR as it does for CA patients. Another conclusion was that response rates differed markedly between patients in both races with high initial levels of HCV RNA. This was consistent with prior data but now confirmed that there was a racial element to the poor response shown by those with high RNA levels. The study had a uniform method of recording medication compliance with patients, and showed that 54% of AA patients (compared to 73% of CA) took at least 80% of maximum doses of interferon and ribavirin (p< 0.001).

Both insulin resistance and interferon signaling stand independently as factors that affect SVR. In addition, they may explain why AA patients respond less well to treatment. Molecular evidence has identified certain genes and proteins involved in insulin resistance and interferon signaling in relation to HCV infection. Microarray analysis using liver biopsy tissue can

determine the expression and significance of these proteins and allow construction of gene pathways unique to these processes. Such analysis can also generate gene lists and pathways for different outcomes such as viral response at day 28.

Essentially, a gene signature for any potential process may be created and compared to other signatures to find genes of interest.

HCV infection may induce an insulin-resistant state. This may be mediated by both HCV structural and

nonstructural proteins. (20) Core proteins have been shown to inhibit peroxisome proliferator-activated receptor alpha (PPAR-a) and PPAR-g. Enzymes made by these genes allow proper metabolism of triglycerides and lipids. Triglyceride accumulation promotes the loss of adiponectin receptors in the liver, which coupled with a decrease in circulating adiponectin, leads to systemic insulin resistance. Nonstructural proteins increase reactive oxygen species, which activate nuclear transcription of cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin-6 (IL-6). TNF-a upregulates leptin and downregulates adiponectin. Glucose transporter gene expression is downregulated through TNF-a actions on insulin receptor substrate 1, 2 (IRS1, 2). Overall, a state of hyperinsulinemia and hyperglycemia is perpetuated. IL-6 promotes hepatic insulin resistance through an acute phase response. Due to high circulating levels, it may promote insulin resistance in other tissues besides the liver. These cytokines also initiate a steatotic response in the liver. HCV infection directly alters insulin cell signaling as well. (21) This was studied by exposing liver tissue to insulin and subsequently using immunoprecipitation and Western Blot analysis to identify proteins. Significant findings included a defect in the post-receptor reaction between insulin receptor substrate-1 (IRS-1) and the insulin receptor in HCV-infected subjects. Also seen were defects in specific pathways

that allow insulin to have a metabolic effect on tissue. See Table 2.

Gene expression studies of interferon signaling have shown that poor initial response to treatment, as well as lower SVR, can be linked to higher expression of interferon

stimulated genes (ISG) pretreatment. (22-24) Strong activation of interferon pathways at baseline weakens induction of ISG during treatment. An exciting breakthrough occurred when a genetic polymorphism near the IL-28B gene was identified. The IL-28B gene encodes IFN-I, which likely induces Jak-Stat pathway

Action	Effect
Inhibit PPAR-a, PPAR-g	Increase triglycerides → Decrease liver adi-
Increase reactive oxy-	Increase TNF-a, IL-6
Increase TNF-a	Increase leptin, decrease adiponectin Decrease glucose transporter gene
Increase IL-6	Acute phase response in liver, hepatic insu-
Alter insulin receptor	Decrease insulin sensitivity with its receptor

responses to induce antiviral resistance. (25, 26) This polymorphism was found to be strongly associated with SVR in all patient groups. (25) Patients of European ancestry had high genome-wide significance for the polymorphism ($p=1.06 \times 10^{-25}$). One particular genotype, CC, had a two-fold greater rate of SVR than another genotype, TT, in patients of European ancestry (95% CI, 1.8-2.3). Similar ratios were seen in patients of African and Hispanic ancestry. The C allele was also linked to higher baseline viral loads, which previously was thought to hinder treatment response. The allele may play a role in intrahepatic ISG, which complicates previously held beliefs about levels of viral load and treatment response.

Current research focuses on linking the molecular evidence of HCV infection and associated processes, such as insulin resistance, to pathways that may explain treatment disparities. For instance, using a subset of patients from the VIRAHEP-C study, a list of genes with significant expression difference between patients with and without insulin resistance can be generated. This list is controlled for confounders such as body mass index, steatosis and fibrosis. The list can be mined for known pathways that may further elucidate the steps involved in insulin resistance. These pathways may then be compared to pathways generated for other variables, such as SVR in CA or SVR in AA. Early work at the University of Maryland, Baltimore has found that interferon pathway genes are shared between signatures for race and viral response at day 28. This has led to the observation that upregulated interferon pathway genes pretreatment are more common in AA patients.

FUTURE TREATMENTS AND CONCLUSION

The next generation of HCV treatment is termed Specifically Targeted Antiviral Therapy against HCV (STAT-C). Phase II studies have shown promising results for protease inhibitors. Telaprevir, when used in combination with PEG-IFN and ribavirin, has demonstrated a clear increase in EVR and SVR in genotype 1 patients. (27) The role of ribavirin has been validated as well, confirming a reduction in breakthrough and relapse rates despite the drug's toxic side effect profile. (28) Another protease inhibitor, Boceprevir, has finished phase II study. Future drug therapies may include polymerase inhibitors, nucleoside analogues and nonnucleoside analogues. While PEG-

IFN and ribavirin remain the standard of care, future approaches will add new agents onto this regimen. In addition, a patient's genotype for certain processes, separate from their HCV genotype, may dictate the initial therapy chosen. The strongest current example is the presence of the IL-28B polymorphism. Such host-specific considerations, along with increased diagnosis of the virus, will diminish the morbidity and mortality of chronic HCV infection.

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REFERENCES

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; 16;144 (10):705-714.
2. Dienstag JL, McHutchison JG. American Gastroenterological Association technical review on the management of hepatitis C. *Gastroenterology* 2006; 130 (1):231-264.
3. Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. *Hepatology* 2002; 36 (5 Supp 1): S1-2.
4. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. *Lancet* 2001;358 (9286):958-965.
5. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *NEMJ* 2002; 26;347 (13):975-982.
6. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; 140(5):346-355.
7. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of chronic hepatitis C infection. *NEMJ* 2009; 361(6):580-593.
8. Camma C, Di Bona D, Schepis F, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. *Hepatology* 2004; 39(2):333-342.
9. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in

- patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007; 147(10):677-684.
10. Shiffman ML, Morishima C, Dienstag JL, et al. Effect of HCV RNA suppression during peginterferon alfa-2a maintenance therapy on clinical outcomes in the HALT-C trial. *Gastroenterology* 2009; 137(6):1986-1994.
 11. Sulkowski MS. Viral hepatitis and HIV coinfection. *J Hepatol* 2008; 48(2):353-367.
 12. Sterling RK, Contos MJ, Smith PG, et al. Steatohepatitis: risk factors and impact on disease severity in human immunodeficiency virus/hepatitis C virus coinfection. *Hepatology* 2008; 47(4):1118-1127.
 13. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA* 2010; 304(3):321-333.
 14. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. *J Gastroenterol Hepatol* 2008; 23(4):512-520.
 15. Liu CJ, Chuang WL, Lee CM, et al. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis B and C viruses. *Gastroenterology* 2009; 136(2):496-504.
 16. Terrault NA. Hepatitis C therapy before and after liver transplantation. *Liver Transpl* 2008; Suppl 2:S58-66.
 17. Gallegos-Orozco JF, Yosephy A, Noble B, et al. Natural history of post-liver transplantation hepatitis C: a review of factors that may influence its course. *Liver Transpl* 2009; (12):1872-1881.
 18. Everson GT. Should we treat patients with chronic hepatitis C on the waiting list? *J Hepatol* 2005; 42(4):456-462.
 19. Conjeevaram HS, Fried MW, Jeffers LJ, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 2006; 131(2):470-477.
 20. Sheikh MY, Choi J, Qadri I, Friedman JE, Sanyal AJ. Hepatitis C virus infection: molecular pathways to metabolic syndrome. *Hepatology* 2008; 47(6):2127-2133.
 21. Aytug S, Reich D, Sapiro LE, Bernstein D, Begum N. Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. *Hepatology* 2003; 38(6):1384-1392.
 22. Chen L, Borozan I, Feld J, et al. Hepatic gene expression discriminates responders and nonresponders in treatment of chronic hepatitis C viral infection. *Gastroenterology* 2005; 128(5):1437-1444.
 23. Feld JJ, Nanda S, Huang Y, et al. Hepatic gene expression during treatment with peginterferon and ribavirin: identifying molecular pathways for treatment response. *Hepatology* 2007; 46(5):1548-1563.
 24. Sarasin-Filipowicz M, Oakeley EJ, Duong FH, et al. Interferon signaling and treatment outcome in chronic hepatitis C. *Proc Natl Acad Sci USA* 2008; 105(19):7034-7039.
 25. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461(7262):399-401.
 26. Kotenko SV, Gallagher G, Baurin VV, et al. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol* 2003; 4(1):69-77.
 27. Asselah T, Benhamou Y, Marcellin P. Protease and polymerase inhibitors for the treatment of hepatitis C. *Liver Int* 2009; 29 Suppl 1:57-67.
 28. Shiffman ML. What future for ribavirin? *Liver Int* 2009; 29 Suppl 1:68-73.

In Review:

Screening for Thyroid Disease

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INTRODUCTION

The merits of population-wide screening for thyroid disease remain debatable. As clinicians we decide which patients to screen for thyroid disease, at what age, and with what frequency. In addressing that question, we must weigh the benefits of identifying and treating individuals with thyroid disease against the associated costs and/or harm of doing so. Given the range of symptoms and their severity on initial presentation, many patients will be unaware of having thyroid disease unless they are identified by screening. If not identified through screening, these patients are at risk for complications of untreated thyroid disease. To further complicate identification of thyroid disease, when symptoms are reported, they are frequently confused with other health problems.

The manner in which physicians identify whom to screen is unsettled, as well. Vaidya et al. studied a population of pregnant women and found that detection of thyroid disease by case-finding alone missed up to one third of women with hypothyroidism. (1) On one hand, early diagnosis may be associated with positive outcomes. For example, in hypothyroidism, treatment can lead to decreased serum cholesterol and subsequent reduction in prevalence of heart disease. (2) On the other hand, we must consider the cost of screening. One estimate, based on screening women every 5 years starting at age 35 years, indicated a cost of screening of \$9,200 per quality-adjusted year of life. Most of the benefit was attributed to preventing progression into overt hypothyroidism and its associated morbidity.

Recognizing the risks of undiagnosed thyroid disease and the acceptable cost per quality-adjusted year of life,

professional organizations have published screening guidelines for thyroid disease. The American Thyroid Association (ATA) promotes screening beginning at the age of 35 years and every 5 years thereafter. (3) Other expert opinion bodies have advised that screening for thyroid disease should be carried out only on a case-by-case basis, depending on the risk factors and clinical circumstances (e.g., age, pregnancy and presence of risk factors). For example, the American Association of Clinical Endocrinologists (AACE) states that aggressive case-finding is appropriate in high-risk patients such as pregnant women and women older than age 60. (4) The American College of Physicians (ACP) recommends screening women older than 50 years of age who present with symptoms consistent with thyroid disease. On the other hand, the United States Preventive Services Task Force (USPSTF) has found insufficient evidence for or against screening. In addressing this debate, it is important to understand the risk factors associated with thyroid disease along with the consequences of untreated thyroid disease so that physicians can make a well-reasoned decision when choosing which patients to screen for thyroid disease.

Screening Tests for the Detection of Thyroid Dysfunction

The major thyroid hormone secreted by the thyroid gland is thyroxine, also known as T4. T4 is considered a 'prohormone' as it is converted to the more metabolically active triiodothyronine (T3), which is primarily responsible for the tissue effects of thyroid hormone. Approximately 80% of circulating T3 is derived from the monodeiodination of T4, with the remaining 20% being produced directly by the thyroid gland. Both T4 and T3 circulate in the blood, most of

which are bound to transport proteins, with only a very small fraction being free. It is the free fraction that binds to peripheral tissue receptors and exerts the metabolic effects of the hormones. Through a classic negative-feedback system, thyroid-stimulating hormone (thyrotropin; TSH), produced in the pituitary gland, controls the amount of T4 or T3 produced by the thyroid gland. Because of the exquisite sensitivity of the negative-feedback system, the single most important diagnostic test for thyroid dysfunction is the measurement of the serum TSH, which is both sensitive and specific. TSH levels are increased in patients with primary and subclinical hypothyroidism. TSH levels will be decreased in patients with primary and subclinical hyperthyroidism. Central hypothyroidism can have normal or low TSH, and TSH-mediated hyperthyroidism can have normal or high TSH. If the TSH value is outside the normal reference range, further work-up can then be pursued, which often includes measurement of free T4 and T3 to confirm the diagnosis.

Measurements of free T4 and T3 levels is generally preferred over measurement of total levels of T4 or T3, because total levels may be altered by clinical conditions such as hepatitis, pregnancy and nephrotic syndrome (5) and by numerous medications that interfere with the binding of thyroid hormones to their transport proteins. Both serum total and free T4 are decreased in all forms of primary hypothyroidism. Measurement of serum T3 is less useful and is within the normal range in the majority of patients with hypothyroidism. This may be due to a relatively augmented rate of conversion of available circulating T4 to T3 in peripheral tissues in hypothyroidism, or to the relative preponderance of T3 over T4 secretion from the thyroid as a response to elevated serum levels of TSH in hypothyroidism. As a result, in hypothyroidism, T3 is usually the last level to fall. (6) Patients with hyperthyroidism should have high free T4 and T3 levels. In contrast to the lack of utility of serum T3 measurements in hypothyroidism, measurement of either total or free concentrations of T3 is often useful for the diagnosis of hyperthyroidism.

HYPOTHYROIDISM

Definition of Hypothyroidism

Hypothyroidism results from decreased secretion of

thyroid hormone from the thyroid gland.

Hypothyroidism is most commonly caused by an intrinsic problem within the thyroid gland itself, which is termed 'primary hypothyroidism'. Causes of primary thyroid failure include Hashimoto's thyroiditis, subacute, silent and postpartum thyroiditis, iodine deficiency or excess, surgical thyroidectomy, radioiodine (I-131) treatment, external irradiation, infiltrative disorders, drugs that interfere with thyroid function and developmental abnormalities such as agenesis and dysgenesis of the thyroid. More rarely, hypothyroidism can also result from TSH deficiency, termed 'secondary hypothyroidism', or disorders of the hypothalamus, which have been called 'tertiary hypothyroidism'.

Definition of Subclinical Hypothyroidism

Subclinical hypothyroidism occurs when there is early or mild thyroid failure, evidenced by increased serum TSH levels, but normal free T4 and T3 levels. Progression of disease from sub-clinical to overt hypothyroidism has been demonstrated to occur in approximately 3 to 18% of affected patients per year [7].

Prevalence

Subclinical hypothyroidism is more prevalent than overt hypothyroidism. Data from the United States National Health and Nutrition Examination Survey (NHANES III) found the prevalence of overt hypothyroidism to be 0.3%, while the prevalence of subclinical hypothyroidism was 4.3%. (8) In the Colorado Health Fair survey, the prevalence of overt and subclinical hypothyroidism was 0.4 and 9.0%, respectively. (9)

Clinical Manifestations

Since thyroid hormone receptors exist in virtually every tissue of the body, the signs and symptoms of hypothyroidism can affect almost any organ system. Patients may complain of feeling tired, depressed, cold or forgetful. They may experience weight gain, constipation, dry skin and muscle cramps. Younger women may suffer menstrual irregularities and infertility, and pregnant women with hypothyroidism are at a greater risk of miscarriage and other obstetric complications. Upon physical examination, patients

may have a goiter, speak slowly and in a low-pitched, hoarse voice, and exhibit bradycardia, lower extremity edema and delayed deep tendon reflexes. These symptoms are quite common in, and suggestive of, frank thyroid hormone deficiency. Although paradoxical, approximately 30% of those with subclinical disease present with these symptoms. (7)

Complications of Hypothyroidism

Hypothyroidism can lead to decreased cardiac output, hypertension, hypercholesterolemia, sleep apnea, anemia, and various metabolic abnormalities.

Risk Factors for Hypothyroidism

It is important for physicians to be aware of the risk factors for hypothyroidism in order to identify which patients are most appropriate for screening.

Gender, age & race

The risk for development of hypothyroidism increases with age, and approximately eight to ten times more women than men are affected. Some reports have indicated that the prevalence of subclinical hypothyroidism in women older than 60 years is approaching 20%. (2) Hypothyroidism is most commonly seen in Caucasians. Data from the NHANES III showed the prevalence of subclinical hypothyroidism to be 5.8% among white non-Hispanic women, 5.3% among Mexican-American women, 1.2% among black, non-Hispanic women, 3.4% among white men, 2.4% among Mexican-American men and 1.8% among black men. (8)

Personal history of autoimmune disorders

Those with a personal history of an autoimmune disorder are at increased risk for the development of other autoimmune disorders, such as Hashimoto's thyroiditis. Autoimmune polyendocrine syndromes are a group of diseases characterized by autoimmune activity against more than one endocrine organ. In patients presenting with a single endocrine autoimmune disorder who are at genetic risk for a polyendocrine syndrome, the prevalence of a subsequent additional autoimmune disorder is 30 to 50-times that of the general population. (14) Autoimmune thyroid disease, or Hashimoto's thyroiditis, is part of

autoimmune polyendocrine syndrome type 2, which is characterized by Addison's disease, autoimmune thyroid disease, Type 1 diabetes and, less commonly, vitiligo and hypogonadism. There is general consensus that patients with at least one autoimmune disorder should have yearly TSH screening if autoantibodies against thyroid peroxidase are present, or that patients should undergo TSH screening every five years if autoantibodies are absent. (14)

Of all autoimmune disorders, the most frequent association observed is between Type 1 diabetes mellitus and autoimmune thyroid disease. Cross-sectional studies have reported a prevalence of hypothyroidism in 12 to 24% of women and 6% of men with Type 1 diabetes. (15) The AACE recommends that TSH levels be checked at regular intervals in patients with Type 1 diabetes. (4)

The most common autoimmune disorder associated with vitiligo is thyroid disease. (16) Hashimoto's thyroiditis is 2.5 times more frequent among children and adolescents with vitiligo than in a healthy age- and sex-matched population. (17) It has been proposed that patients with vitiligo receive annual screening for thyroid dysfunction. (18)

Autoimmune thyroid disease is the most common autoimmune disorder associated with primary adrenal insufficiency and has been found in approximately 20% of these patients. (19,20) Therefore, it is recommended that patients with autoimmune or idiopathic Addison's disease be screened periodically for the development of thyroid disease, with TSH measurement occurring at least annually. (14)

Patients with autoimmune thyroid disease and positive serum anti-thyroperoxidase antibodies are more likely to have antigastric parietal cell antibodies as well. As many as 24% of Caucasians with pernicious anemia may have autoimmune thyroid disease. (21) There is consensus that it is reasonable to be vigilant about the risk of hypothyroidism in patients with pernicious anemia and to perform a screening of TSH levels annually.

Family history of autoimmune disease

Family members of those with almost any non-thyroidal autoimmune disease are at increased risk for developing autoimmune thyroid disease as well. It is recommended that relatives of patients with multiple autoimmune endocrine disorders be evaluated

medically and undergo screening with TSH measurement every three to five years. [22].

Personal history of thyroid disease

Having a personal history of thyroid disease increases the risk of subsequently developing more permanent thyroid disease. For example, approximately 30% of patients with postpartum thyroiditis will ultimately develop permanent thyroid failure. (23,24) It is recommended that an annual TSH level test be performed in those with a history of postpartum thyroiditis (25)

Family history of thyroid disease

A family history of thyroid disease, especially in a first degree relative, increases the risk for developing thyroid disease. For example, Hashimoto's thyroiditis clusters in families, and the concordance rate in monozygotic twins is 30 to 60%. (26) It is therefore essential to obtain a family history of both endocrine and autoimmune disease in new patients and to then screen those individuals with a positive family history of thyroid disease with a serum TSH level test on an annual basis thereafter.

External irradiation to the neck

The thyroid gland can be very sensitive to damage from radiation such as that given for Hodgkin's disease, and patients with a history of external irradiation to the neck are at increased risk for development of hypothyroidism. Ozawa et al. found the incidence of hypothyroidism in those with head and neck cancer treated with radiation alone to be 32%, while in those treated with both radiation and surgery, the incidence was 46%. (27) It is recommended to perform a routine annual check of thyroid function in patients with a history of external radiotherapy to the head and neck.

Thyroidectomy

Inevitably, anyone who has undergone a total thyroidectomy will develop hypothyroidism. The development of symptomatic hypothyroidism should be expected within weeks after total thyroidectomy. However, onset of symptoms after subtotal thyroidectomy is variable. Screening these patients is important because the majority of surgeons do not place these individuals on supplemental levothyroxine after surgery. McHenry et al. observed hypothyroidism in 35% of their patients after subtotal thyroidectomy. (28)

The duration of any latency between subtotal thyroidectomy and the development of hypothyroidism depends on the integrity or normalcy of the residual thyroid tissue. Thus, hypothyroidism may not occur following lobectomy for a benign nodule in an otherwise normal thyroid gland, whereas eventual hypothyroidism is more likely in a gland with underlying Hashimoto's disease in the contralateral remaining lobe.

I-131 therapy

As with external radiation, internal radiation such as I-131 therapy greatly increases the risk for hypothyroidism. The incidence of post-radioiodine hypothyroidism depends upon several factors, such as the size of the thyroid, radioiodine dose, fractional uptake of radioiodine by the gland and the history of prior antithyroid drug therapy. On average, the incidence of thyroid damage from radioiodine that requires thyroid hormone replacement after one year is approximately 25%. After the first year, an additional 5% of these patients are estimated to develop hypothyroidism per year. (29)

Iodine deficiency

Iodine deficiency, though rare in the United States, is the most common cause of hypothyroidism worldwide, with or without associated goiter. The areas most severely affected include the Western Pacific, South-East Asia and Africa. Physicians should be aware of a possible history of iodine deficiency as the cause of goiter in individuals from these parts of the world.

Iodine excess

Iodine-induced hypothyroidism can occur after administration of iodine-containing radiographic contrast media, the use of drugs rich in iodine such as amiodarone and from dietary sources such as seaweed. Through the so-called Wolff-Chaikoff effect, iodine excess can inhibit iodide organification in the thyroid gland and therefore synthesis of T4 and T3. This vulnerability to iodine-induced hypothyroidism is most commonly found in patients with autoimmune thyroiditis or those previously treated for thyroid diseases, but iodine-induced hypothyroidism can occur, albeit rarely, in those without underlying thyroid disease.

Infiltrative diseases

Thyroid function will be compromised by a reduction in the functioning mass of thyroid tissue, as may occur with infiltrative disorders of the gland. Thus, patients with hemochromatosis, scleroderma, leukemia or metastatic cancer are at increased risk for hypothyroidism. Hypothyroidism in men with hemochromatosis was found to occur at a rate approximately 80 times higher than in unaffected males in the general population. (30)

Cigarette smoking

Women with hypothyroidism who smoke tobacco have been demonstrated to have more severe clinical symptoms than those who do not smoke. The mechanism for this effect is unknown. Smoking has been demonstrated to reduce the secretion of thyroid hormone in women with subclinical hypothyroidism. (31)

Medications

Methimazole and propylthiouracil are antithyroid drugs of the thiourea family that are used routinely in the treatment of hyperthyroidism. In relatively high doses, either can lead to hypothyroidism by excessively decreasing thyroid hormone synthesis. Side effects of other drugs include interfering with the absorption of levothyroxine in patients being treated for hypothyroidism. These agents bind thyroid hormone to their surface and thereby inhibit the effective absorption of thyroid hormone, which will then pass through the gastrointestinal tract unabsorbed. Examples of medications with this effect are cholestyramine, antacids, calcium supplements and sucralfate. A different effect may be seen in medications that suppress TSH and cause secondary hypothyroidism, such as dopamine and corticosteroids. Other medications can cause destructive thyroiditis, such as amiodarone and sunitinib. Amiodarone can also cause an iodine-induced hypothyroidism, especially in patients with Hashimoto's disease, and drug-induced hypothyroidism may also occur with treatment with lithium and certain antiretroviral agents.

HYPERTHYROIDISM*Definition of Hyperthyroidism*

Hyperthyroidism results from increased levels of circulating thyroid hormone. The most common cause is

Graves' disease. Other causes include toxic adenoma, toxic multinodular goiter, painful subacute thyroiditis and silent thyroiditis. Rare causes include TSH-secreting pituitary adenomas, struma ovarii, meta-static functioning thyroid cancer and metastatic (nonthyroidal) tumors within the thyroid gland.

Definition of Subclinical Hyperthyroidism

The combination of a serum TSH concentration below the lower limits of the reference range and normal levels of serum T4 and T3 is known as subclinical hyperthyroidism. Such patients may often have some degree of underlying autonomous function in their thyroid gland. The degree of hyperfunction may be enhanced by exposure to excess iodine or may simply progress with time. For example, in patients with multinodular goiter, Wiersinga found the estimated rate of progression from subclinical to overt hyperthyroidism to be 5% each year. (32)

Prevalence

Data from the NHANES III indicate that the prevalence of overt hyperthyroidism was 0.5%, while the prevalence of subclinical hyperthyroidism was 0.7%. (8) In the Colorado Health Fair survey, the prevalence of overt and subclinical hyperthyroidism was 0.1 and 2.1%, respectively. (9) Prevalence differs depending on factors including gender, the mean age of population, geography and average iodine intake.

Clinical Manifestations

Typical symptoms of hyperthyroidism include weight loss, heat intolerance, agitation, anxiety, weakness and difficulty with concentration and memory. Patients may describe weight loss despite increased appetite, palpitations, an increased frequency of bowel movements and irregularity to their menstrual cycles. Upon examination they may demonstrate tachycardia, warm skin, a strong cardiac apical impulse, hand tremors and relatively brisk, deep tendon reflexes.

Complications of Untreated Hyperthyroidism

Hyperthyroidism can lead to increased myocardial oxygen demand, coronary artery spasm, coronary ischemia, CHF, osteoporosis, neuropsychiatric dysfunction and increased risk for arrhythmias, especially atrial fibrillation.

Risk Factors for Hyperthyroidism

Gender & age

The NHANES III revealed the prevalence of hyperthyroidism in women to be approximately 1 to 2% and approximately a tenth of this number in men. Graves' disease has a female-to-male incidence ratio of approximately 7–10:1. (37) Graves' disease is the most common cause of spontaneous hyperthyroidism in patients younger than 40 years of age, and this risk does not change with age. By contrast, hyperthyroidism associated with a multinodular goiter typically presents in individuals older than 50 years of age, and hyperthyroidism due to a solitary toxic nodule usually presents in the third or fourth decade of life. (37)

Personal & family history of autoimmune disorders

Patients with a nonthyroidal autoimmune disorder and their family members have an increased frequency of other autoimmune disorders, such as Graves' disease. For example, autoimmune thyroid disease is observed in 25% of Type 1 diabetics, and approximately 3% of patients with Graves' disease have pernicious anemia. (37) It is important to be attentive to screening for thyroid disease in patients who present with other autoimmune disease.

Family history of thyroid disease

There is a significant clustering of thyroid disease in families, with 40 to 50% of patients reporting another family member with thyroid disease. (37,38) There is a strong hereditary component to Graves' disease, with a concordance rate of Graves' disease in monozygotic twins of 30 to 40%, compared to less than 5% among dizygotic individuals. (39)

Iodine excess

Exposure to an iodine load may lead to the development of iodine-induced hyperthyroidism in patients with underlying nodular thyroid disease or indolent Graves' disease. Hyperthyroidism precipitated by iodine excess has been called the Jod-Basedow effect or phenomenon. This occurs more frequently in areas with endemic iodine deficiency, but it is also common in iodine-replete regions such as North America. The possible sources of iodine excess are similar to those listed previously for iodine-induced hypothyroidism. In the case of the drug amiodarone, which is 37% iodine by weight, either an iodine-induced thyrotoxicosis (type

I) or an amiodarone-induced destructive thyroiditis with thyrotoxicosis (type II) may occur.

Cigarette smoking

Cigarette smoking has been demonstrated to increase the risk for Graves' disease and Graves' ophthalmopathy. The relationship is both dose- and time-dependent, with current smokers having a higher risk than ex-smokers. There is a direct relationship between the number of cigarettes smoked and the severity of ophthalmopathy.

Medications

Amiodarone can cause thyrotoxicosis owing to the iodine load (type I) in patients with any cause for underlying autonomously functioning thyroid tissue, such as solitary functioning adenomas, multinodular goiter or Graves' disease. The destructive thyroiditis caused by amiodarone (type II) can be quite severe and difficult to treat but is usually self-limiting. Disruption of the thyroid follicular cells leads to the acute release of T4 and T3, a process that ceases after the gland's hormonal stores are depleted.

Lithium carbonate has been used in the treatment of hyperthyroidism. The mechanism of its beneficial action is inhibition of T4 and T3 release from the thyroid gland, similar to the action of iodine. Paradoxically, lithium can cause thyrotoxicosis by inducing a form of silent thyroiditis. Other agents such as IFN- α and IL-2 are associated with increased thyroid autoimmunity, which may result in hyperthyroidism. IFN- α can also cause thyrotoxicosis by inducing a destructive thyroiditis.

CONCLUSION

A strong case can be made for screening for thyroid dysfunction in a wide variety of circumstances. If left untreated, hypothyroidism and hyperthyroidism carry significant morbidity and potential mortality. With any disease screening process, the primary focus needs to first and foremost address susceptible individuals or populations at risk. It is important to elicit a meticulous history from each patient to determine that individual's risk for thyroid disease and, therefore, the importance of screening. It is reasonable to have a lower threshold for screening for thyroid disease in women, especially after the age of 40, and in those with a personal and family history of autoimmune disease, as well as those with a

family history of thyroid disease. Furthermore, it is important to examine patients' medication lists to identify any use of those agents associated with a greater risk of thyroid disease. Successful identification of either subclinical or overt thyroid disease through screening allows us to diagnose patients earlier and potentially prevent complications of their disease.

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REFERENCES

- Vaidya B, Anthony S, Bilous M et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 2007; 92(1): 203–207.
- Cooper DS. Subclinical hypothyroidism. *NEMJ* 2001; 345(4): 260–265.
- Ladenson PW, Singer PA, Ain KB et al. American thyroid association guidelines for detection of thyroid dysfunction. *Arch Intern Med* 2000; 160(11): 1573–1575.
- Surks MI, Ortiz E, Daniels GH et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; 291(2): 228–238.
- Nayak B, Hodak SP. Hyperthyroidism. *Endocrinol. Metab Clin. North Am* 2007; 36 (3): 617–656.
- Larsen PR, Davies TF, Schlumberger MJ, Hay ID. Chapter 10 – thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: *Kronenberg: Williams Textbook of Endocrinology (11th Edition)* 2008; Saunders Elsevier, PA, USA 299–332.
- McDermott MT, Ridgway EC. Clinical Perspective: subclinical hypothyroidism is mild thyroid failure and should be treated. *J. Clin Endocrinol Metab* 2001; 86(10): 4585–4590.
- Hollowell JG, Staehling NW, Flanders WD et al. Serum TSH, T(4), and thyroid antibodies in the united states population (1988 to 1994): national health and nutrition examination survey (NHANES III). *J Clin Endocrinol Metab* 2002; 87(2): 489–499.
- Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; 160(4): 526–534.
- Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. *Ann Intern Med* 2000; 132(4): 270–278.
- Duntas LH, Wartofsky L. Cardiovascular risk and subclinical hypothyroidism: focus on lipids and new emerging risk factors. what is the evidence? *Thyroid* 2007; 17(11): 1075–1084.
- Meier C, Staub JJ, Roth CB, Guglielmetti M et al. TSH-controlled l-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (basel thyroid study). *J Clin Endocrinol Metab* 2001; 86 (10): 4860-4866.
- Rodondi N, Newman AB, Vittinghoff E, Rekeineire N et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Int Med* 2005; 165 (21): 2460-2466.
- Eisenbarth GS, Gottlieb PA. Medical progress: autoimmune polyendocrine syndromes. *NEMJ* 2004; 350 (20): 2068–2079.
- Umpierrez GE, Latif KA, Murphy MB et al. Thyroid dysfunction in patients with Type 1 diabetes. *Diabetes Care* 2003; 26(4): 1181–1185.
- Owen JC, Cheetham TD. Diagnosis and management of polyendocrinopathy syndromes. *Endocrinol Metab Clin North Am.* 2009; 38(2): 419–436.
- Kakourou T, Kanaka-Gantenbein C, Papadopoulou A, Kaloumenou E, Chrousos GP. Increased prevalence of chronic autoimmune (Hashimoto's) thyroiditis in children and adolescents with vitiligo. *J Am Acad Dermatol* 2005; 53(2): 220–223.
- Taïeb A, Picardo M. Vitiligo. *NEMJ* 2009; 360(2): 160–169.
- Bornstein SR. Current concepts: predisposing factors for adrenal insufficiency. *NEMJ* 2009; 360(22): 2328–2339.

