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UF UNIVERSITY of FLORIDA
College of Medicine
Jacksonville

FOCUS
Page 2

GME CORNER
Page 4

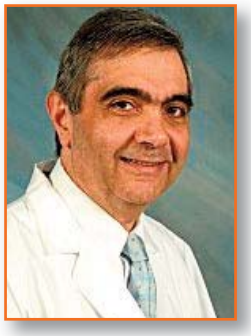
CLINICAL CASE
Page 5

RX UPDATES
Page 7

NEWS & NOTES
Page 8

CHAIRMAN'S MESSAGE

Dear Colleagues:



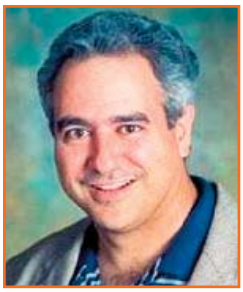
As we embark on a new academic year, it is customary for the department to reflect on the achievements of the past year. The faculty in the department once again excelled in their mission of clinical care and scholarly efforts. Eighteen faculty members received the 2014 University of Florida-College of Medicine's Exemplary Teacher Award. This award is given in recognition of outstanding teaching contributions of individual faculty members.

The Department of Medicine once again had a successful presence at the Research Day on May 15th, 2014. About 37 percent of platform and poster presentations of fellows and residents were made by the members of the department. Of the platform presentations, Dr. Alexandra Joseph was the first-place winner and Dr. Shobha Vootukuri received the third place prize. Among the poster presentations, Dr. William Curban was the fourth-place winner. I am very happy to see that the research productivity of our house staff remains excellent.

I invite you to read the focus section of this issue that discusses the latest guidelines for management of hypercholesterolemia. This is an important and timely topic that has clinical relevance in preventing and treating coronary artery disease.

The faculty within the department are looking forward to a new academic year full of opportunities to enhance our standing and visibility within academic institutions.

Arshag D. Mooradian, MD
Professor of Medicine
Chairman, Department of Medicine



By Martin Zenni, MD

Associate Professor of Medicine

Division of Cardiology

Department of Medicine

The 2013 ACC/AHA Guideline in the Treatment of Blood Cholesterol

With great anticipation, the 2013 ACC/AHA Guideline in the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults was published online on November 12, 2013, after nearly a 10-year void*. The guidelines identify those patients age >21 who are at risk and are "most likely to benefit from cholesterol-lowering statin therapy."

What's New in the Guideline?

The new document strongly emphasizes therapeutic lifestyle changes (TLC), which remain the cornerstone component of health promotion for all patients in an effort to prevent atherosclerotic cardiovascular disease (ASCVD). Risk reduction, with the use of cholesterol-lowering drug therapies when indicated, should be employed simultaneously with TLC. The guideline recommends traditional strategies to reduce risk with TLC by 1) adhering to a heart-healthy diet, 2) promoting regular exercise, 3) smoking cessation and 4) maintenance of a healthy body weight with weight loss 5 to 10 percent of body weight when necessary.

Extensive evidence supporting the use of statins for the prevention of ASCVD in all secondary prevention and high-risk primary prevention groups are recommended. The new guideline focuses not only on fatal and nonfatal myocardial infarction (MI), but also on fatal and nonfatal stroke, which is also a "major burden of disability" that was not included in previous guidelines. The guideline identified six major areas of focus: 1) four STATIN BENEFIT GROUPS, 2) new perspective on LDL-C and/or non-HDL-C treatment goals, 3) global-risk assessment for primary prevention, 4) safety recommendations, 5) role of biomarkers and non-invasive tests and 6) future updates to the blood cholesterol guideline.

Four Major Statin Benefit Groups

Group 1: Patients with clinical ASCVD-secondary prevention, including patients with CAD-angina, ACS, CVA, MI, PCI, CABG, atherosclerotic PAD.

Group 2: Patients with primary elevations in LDL-C > 190 mg/dl (usually genetic cause of high LDL-C)

Group 3: Patients with diabetes mellitus type-1 and type-2, ages 40-75 with LDL-C 70-189 without clinical ASCVD–primary prevention with DM but no known ASCVD

Group 4: Primary prevention patients with an estimated 10-year risk ASCVD > 7.5 percent assessed using a "POOLED COHORT EQUATION" (See below)

Groups 1 & 2: For patients in Groups 1 and 2, High Intensity Statin Therapy (HIST) is recommended for most patients who are candidates. HIST is recommended to lower LDL-C by > 50 percent. Atorvastatin (40-80mg) and Rosuvastatin (20-40 mg) are specifically recommended. For patients who are not candidates for HIST due to comorbidities, safety, or tolerance concerns, Moderate Intensity Statin Therapy (MIST *) is recommended to achieve an LDL-C reduction of 35 to 50 percent. The guideline also recommends MIST for the elderly patients age > 75 primarily for safety concerns. For patients who are at high risk for side effects with comorbidities or statin intolerance, Low Intensity Statin Therapy (LIST**) can be tried in an effort to lower LDL-C by <30%.

MIST*= ATORVASTATIN 10-20 mg, ROSUVASTATIN 5-10 mg, SIMVASTATIN 20-40 mg, PRAVASTATIN 40-80 mg, LOVASTATIN 40 mg, FLUVASTATIN 40 mg BID or 80 mg of the XL, and PITAVASTATIN 2-4 mg

LIST**= SIMVASTATIN 10mg, PRAVASTATIN 10-20 mg, LOVASTATIN 20 mg, FLUVASTATIN 20-40 mg, PITAVASTATIN 1 mg.

Group 3: For diabetic patients without clinically evident ASCVD, MIST is recommended unless the patient's 10-year risk estimate using the POOLED

Continued on Page 3

Focus continued from Page 2

COHORT EQUATION is > 7.5 percent. In this case, HIST is recommended along with TLC and moderate diabetic blood sugar control.

Group 4: For the "primary prevention" patients in Group 4 age 40-75, 10-year ASCVD risk (of fatal/non-fatal MI and fatal/non-fatal stroke) should be assessed. Risk is calculated using the POOLED COHORT EQUATIONS - POOLED COHORT RISK CALCUATOR (PCRC). The web-based calculator can be downloaded at myamericanheart.org/cvriskcalculator. The Excel-based calculator allows a provider to calculate 10-year and lifetime risk of ASCVD events for a patient after input of basic clinical and blood cholesterol data. The focus of treatment is to identify those patients most likely to benefit from statin therapy. MIST and HIST are recommended on an individual basis after assessing 10-year risk of ASCVD. The guideline recommends matching the intensity of treatment to risk, while balancing risk-benefit treatment ratios. A frank discussion of statin therapy, patient preference, benefit and risk of SE should always precede therapy, particularly in the elderly age 75 and older who almost always have a 10-year PCRC risk of ASCVD > 7.5 percent based on age alone. Secondary causes of hyperlipidemia should be ruled out and addressed prior to starting statin therapy, e.g. excessive alcohol intake, uncontrolled DM, nephrosis, hypothyroidism, medication SE, etc. For patients at borderline risk, additional testing with cardio CRP (>2mg/L), ABI testing (< 0.9) or calcium scoring (CAC > 300) can be considered to further refine or define risk before deciding on statin therapy. Advanced lipid testing is not recommended.

Limitations

The new guideline "was not intended to be a comprehensive document" with regard to lipid management. With some controversy, specific LDL-C targets were abandoned in the new guideline as the majority of randomized clinical trials (RCT) did not clearly identify what the LDL-C target should be for patients with ASCVD or at risk for it. The "lower is better" LDL-C lowering approach was also abandoned because RCT did not support multi-drug lipid therapy, which is expensive, often risky and without clear evidence of clinical benefit with some suggestion of harm. To date, there are simply no compelling data showing that adding a non-statin lipid lowering medication (i.e. fibrates, nicotinic acid, bile acid sequestrants and ezetimibe) to HIST provides incremental benefit in ASCVD risk reduction (no benefit in AIM-HIGH, ACCORD trials, etc.). Moreover, combination data with the omega-3 fatty acids and statins remains controversial, with more recent studies demonstrating a lack of efficacy and possible increased risk of prostate cancer in men. Finally, the guideline makes "no recommendation with regard to patients with NYHA class III & IV CHF or with ESRD on dialysis. The decision to treat these patients with a statin and at what intensity is left to provider discretion with no clear RCT to support statin therapy to lower ASCVD events (CORONA, GISSI-HF, AURORA trials, etc.). Finally, some experts have argued that the PCRC overestimates risk and should have been more thoroughly tested prior to adoption since the new guidelines are likely to identify millions of Americas at risk.

Monitoring Therapy

The new guideline does greatly reduce the burden associated with treating patients and monitoring statin therapy by simplifying treatment paradigms. The guideline states it is "no longer necessary" to routinely monitor CK and ALT (even after initiating therapy) unless the patient has SE or complaints while on therapy. Serial lipid testing monitoring is greatly scaled back without the need for statin titration, combination therapy, additional screening of blood lipids and routine surveillance of muscle and liver enzymes (CK and ALT). Only a second lipid panel is recommended at four to 12 weeks after initiating therapy to assess patient compliance and not an LDL-C target. In selected patients at risk for SE, they may be screened if they have renal or hepatic impairment, age 75 and older, prior hemorrhagic CVA, or when starting new medications that might interact with statin therapy or when presenting with new muscle symptoms. It is reasonable to monitor patients treated with combination lipid-lowering medications (usually when TG's are > 500 mg/dl to prevent gallstones or pancreatitis), protease inhibitors (HIV), or immunosuppressive medications (transplant patients). Simvastatin 80 mg should be avoided and new DM should be screened for in patients with long-term treatment with a small risk in the

Continued on Page 4

incidence of new DM (about 7 percent). When there is a confounding issue, complication, or SE, the intensity of statin therapy can be reduced with the same statin or a new statin attempted. Once again, LDL-C should not be looked at as a "performance standard or goal" any longer.

Summary

The new guideline is clear and easy to implement although one must download the new Cohort Pooled Risk Calculator. Treating high-risk patients with TLC and HIST makes sense since these patients derive the largest absolute and relative risk reduction in preventing ASCVD events. HIST is recommended for patients with known clinical ASCVD (Group 1), familial hyperlipidemia LDL-C > 190 md/dl (Group 2), and high-risk patients with DM (some patients in Group 3). Moderate risk patients (Groups 3 and 4) should receive MIST along with patients age 75 and older, or those unable to tolerate HIST. LIST is reserved only for those patients who cannot tolerate HIST or MIST, or for those patients who are at low risk and statin therapy is agreed upon.

Final Comments

I expect it will be arduous for many providers and highly motivated patients to back away from the treatments goals we have mandated over the past decade. I expect it will also be difficult for some providers and patients to scale back and move away from combination therapy, particularly when it is has been successful. Patients in Group 4 and some in Group 3 remain a challenge for the practitioner because global risk assessment is necessary prior to starting therapy, usually TLC with MIST. In all cases, treatment should pass the "litmus test" in matching intensity of statin therapy to risk in a way that makes sense on a case-by-case review. The guidelines are made to "guide" clinical judgment at the bedside and not replace it, especially for younger patients who have a low 10-year risk of ASCVD but elevated lifetime risk of developing ASCVD. There will be much to discuss going forward and many patients questioning the new guideline and changes in treatment paradigms that we have ingrained in them and ourselves. I can be reached by email at martin.zenni@jax.ufl.edu if you have questions.

** In developing the document, the NHLBI turned over control of the guideline to the ACC / AHA which published the document with collaboration from many specialties and with collaboration from many organizations. The diverse panel of 16 members and 27 peer reviewers took great care to ask relevant clinical questions and then answer them with the available evidence in 2011. They relied primarily on and made recommendations derived from randomized clinical trials. Meta-analyses and observational studies were evaluated for quality and were excluded when the scientific weight of evidence was not sufficient. The guidelines identify those patients older than 21 years of age who are at risk and are "most likely to benefit from cholesterol-lowering statin therapy." Of note, the National Lipid Association (NLA) participated but did not endorse the document as "guidelines," calling the document "important and constructive, but does not go far enough to address gaps in clinical care."*

GME CORNER

Jeffrey House, DO, MPH

Associate Professor of Medicine
Division of General Internal Medicine

Program Director,
Internal Medicine Residency

A Perspective on the Incoming Class for Internal Medicine Here and Abroad

Another recruiting season has gone by and the Internal Medicine program welcomes what we expect to be another fantastic class to join us in the upcoming academic year. With almost 5,000 applicants this year, it was no easy task for the GME leadership to decide on the candidates who best fit our vision. This marks the greatest interest we've had from candidates since our record through the NRMP. After an inordinate amount of time reviewing applications, the program set out to interview 204 applicants, with 176 of them being categorical applicants. After 25 very busy interview days, and several days of painstaking work formalizing the rank list, we were ready for the match. When match day finally came, we were very excited with the results.

Continued on Page 5

GME Corner continued from Page 4

The incoming class of 2017 is comprised of very talented and intelligent individuals. With an average Step 1 USMLE of 232 , this ranks amongst the highest scores our program has ever had. There are interns with MPH degrees, as well as one with an MBA in Health Care Management. We welcome a high number of Osteopathic graduates this year; six in total. Also, we were able to keep several Florida students, including one from the University of Florida, one from Florida International University, and others from Nova Southeastern and Lake Erie College of Osteopathis Medicine. Many of our new interns have had experience at UF Health Jacksonville prior to joining us. In fact, five interns participated in elective rotations here and one had experience working in the research department. It's very telling when one-third of our interns have had in-depth exposure to our program and then end up matching with us. We are very excited about this class and look forward to the academic year that is now upon us.

On a national level, Internal Medicine remains the most popular residency and has enjoyed modest growth over the past several years. In 2014, the number of active applicants was 34,270. That's 85 fewer than in 2013 (34,355), the first decrease since 2003. Despite this, Internal Medicine retained a solid number of applicants with roughly 20 percent of applicants applying to categorical medicine. This year 19 percent of U.S. Seniors matched in Internal Medicine, for a total of 3,167 students. Although only a small increase since last year's match, it represents a greater-than-10-percent increase since 2010.

In 2013, the NRMP enacted the "all-in" policy in which all residency programs had to either accept all of their residents through the match or not participate in the match at all. In response to this policy, the total number of positions increased by 2,399 (9 percent) in 2013 compared to 2012. That increase resulted mainly from expansion of larger specialties such as Internal Medicine, Pediatrics and Family Medicine. Despite some initial concerns from programs around the country, the "all-in rule" has not negatively impacted match rates for Internal Medicine. In fact, 99.1 percent of all categorical residency positions were filled this year. This is more impressive when you take into account that the 6,524 PGY-1 IM positions make up exactly one-quarter of all PGY-1 positions.

Every year is a new and different season for the Match both here and abroad. It won't be long before a new recruiting season is upon us. For now, let's enjoy the opportunity of teaching new, eager young minds.

CLINICAL CASE

Christina Mathai, MD, Internal Medicine Resident
Department of Medicine, UFCOM-Jacksonville

An Unusual Case of Streptococcus Anginosus Cerebral Abscess

Case Presentation

A 30-year-old man presents to UF Health Jacksonville ED with the chief complaint of three days of severe headache associated with photophobia and white spots in vision field. He denied blurry vision, nausea, vomiting, fevers, chills or neck pain. Two weeks ago, he was discharged from a hospital in Ocala after treatment for pneumonia. He was tested for HIV and TB during that stay. He was told the results were negative and was sent home with an oral antibiotic to complete 14 days of therapy.

PMH: migraine headaches and asthma; meds: Excedrin migraine and albuterol; PSH: none; allergies: none; FMH: no known medical illnesses; social history: previous IV drug abuse about 10 years prior. No alcohol use. Cigarette 10 pack years.

Physical exam: (pertinent positives): T = 99.3F, BP = 119/55, HR = 65, RR = 15, 96% RA. General: obese, laying in dim room, appeared in pain; neck: supple, no signs of rigidity; eyes: PERRLA. EOM

Continued on Page 6

Clinical Case continued from Page 6

intact. No ptosis or nystagmus. Corneal reflex intact. Fundoscopic exam: engorged veins, blurred disc margins, sluggish venous pulsation; lungs: noted to be clear bilaterally; neuro: normal sensation, no motor deficits. No CN deficits. Power 5/5 in UE and LE. Romberg negative and gait normal.

Labs: CBC: WBC = 10, Hb = 11, Hct = 36, Plt = 315, N = 65, B = 0; BMP: Na = 138, K = 4.3, Cl = 103, HCO3 = 24, BUN = 6, Cr = 0.6, Gluc = 107; Ca = 8.5, alb = 3.6, AST = 17, ALT = 20, D.BILI = 0.1, I.BILI = 0.2, T.BILI = 0.3, ALP = 77

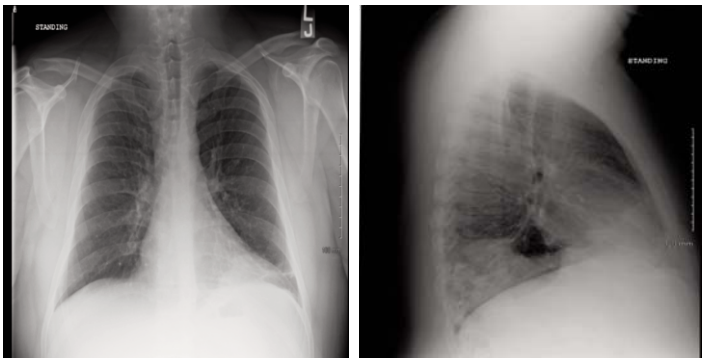


Figure 1: Chest X-ray showing left lower lobe consolidation

CT of head without contrast showed multifocal areas of mixed attenuations at bilateral frontal and occipital lobes. Hemorrhagic components cannot be excluded. Differential considerations include infectious and neoplastic etiologies. If previous history of trauma, parenchymal contusions can also be considered. Associated mass effect is noted in the posterior fossa as described. Right inferior prominent extra-axial space may represent volume averaging, however small subdural collection is also a possibility. (Figure not shown.)

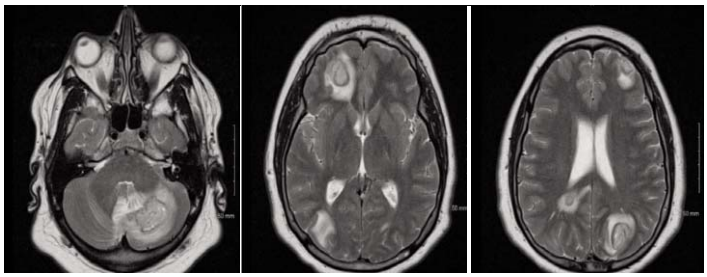


Figure 2: MRI of the brain with and without contrast: multifocal intraparenchymal rim-enhancing lesions and leptomeningeal enhancement. Given clinical scenario, top-differential considerations include infectious versus neoplastic etiologies. Correlation with patient's immune status is advised. Effacement of the fourth ventricle and basal cisterns without evidence of hydrocephalus.

Hospital Course:

Urgent posterior fossa craniectomy and removal of cerebellar lesion was carried out and patient was started on empiric coverage Vanc/Ceftriaxone/Flagyl. Cardiac echo was negative. Gram stain of brain tissue and CSF grew streptococcus anginosus group. The patient was switched to Vanc/Penicillin/flagyl. Neuro ICU course was complicated by diabetes insipidus and elevated ICP requiring EVD. He had tracheostomy placement and frequent returns to OR for stereotactic drainage of abscesses. He developed right common femoral DVT necessitating IVC filter placement. Mental status was improving, ICPs decreased and EVD was clamped. On hospital day 34, the left leg became mottled in color, cold with no palpable pulses. Stat CTA of lower extremeties revealed thrombus in left popliteal artery. He was transferred to OR emergently for thrombectomy and fasciotomy. He experienced refractory hypotension post-op with refractory metabolic acidosis requiring CRRT. Patient had multiple arrests and eventually died.

Discussion

S. anginosus group (aka S. milleri group) is a sub group of viridans streptococci. Consists of three distinct streptococcal species: S. anginosus, S. intermedius and S. constellatus. First isolated in 1956 from dental abscesses and is part of normal flora of oral and GI tract. Ability to cause abscesses sets these streptococci apart from other pathogenic strep species. It is gram-positive, catalase-negative cocci. Non-hemolytic, non-motile, facultative anaerobes.Rapid diagnostic kits and automated systems are available for identification and have been identified in culture-negative brain abscesses using gene sequencing from direct specimens. Often presents as a part of a polymicrobial infection in patients with oral, head and neck, and abdominal infections. Synergy has been shown between members of the S. anginosus group and oral anaerobes. It produces pyogenic exotoxins. S. intermedius produces a cytolytic toxin specific for human cells and the toxin is virulence factor for liver and other deep- seated abscesses. Hydrolytic enzymes such as hyaluronidase play a role in spreading through tissue and liquefaction of pus. Infections range from minor oral infections (den-

Continued on Page7

Clinical Case continued from Page 6

tal abscesses) to life-threatening invasive infection with bacteremia and metastatic abscess formation. Prompt surgical intervention for abscess drainage and IV antibiotics are essential. Treatment for four to six weeks of IV antibiotics include third generation cephalosporins (cefotaxime or ceftriaxone) and metronidazole added for anaerobic coverage. CT follow up at monthly intervals for at least three months for evaluation of therapeutic response. Antibiotic choice should be guided by susceptibility studies (many labs do not perform susceptibility testing for these organisms). Resistance develops easily to fluoroquinolones and therefore are not appropriate for first-line agent. Resistance to aminoglycosides and macrolides is also emerging.

Conclusions:

Although strep anginosus group is part of normal oral and gut flora, it can cause serious and fatal illness if not treated appropriately. Early antibiotics and surgical debridement is key. Evaluation for visceral abscesses or endocarditis is essential when strep anginosus is isolated.

References:

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2)Ruoff KL. Streptococcus anginosus: the unrecognized pathogen. Clin Microbiol Rev 1988; 1:102.
3)Whiley RA, Beighton D. Emended descriptions and recognition of streptococcus constellatus, streptococcus intermedius and streptococcus anginosus as distinct species. Int J Syst Bacteriol 1991; 41:1.

RX UPDATES

Prothrombin Complex Concentrate (Kcentra®)

Reprinted from Drug Update Volume 30, Number 3 Aug – Oct 2013

Prothrombin complex concentrate (PCC), four-factor (Kcentra®) is the first four-factor PCC product available in the United States. This agent was FDA-approved in April 2013 for the urgent reversal of vitamin K antagonist therapy (e.g., warfarin) in patients with an acute major bleed. Three-factor PCC (e.g., Profilnine SD) products have been used off-label for this indication in the U.S.; however, three-factor PCC is only FDA-approved for use in bleeding related to hemophilia B (Factor IX deficiency) patients.

There are several advantages of the new product compared to the three-factor product. First, the four-factor product is able to replace all of the vitamin K-dependent factors inhibited by warfarin (i.e., II, VII, IX, and X, and proteins C and S). Three-factor PCC, contains Factors II, IX, X, but lacks significant quantities of Factor VII. The addition of Factor VII leads to a more rapid and potent reversal of INR compared to three-factor PCC. In 2012, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for Management of Anticoagulant Therapy recommend four-factor PCC for warfarin reversal. Additionally, compared to fresh frozen plasma (FFP), there is no need to thaw the product or match the patient's blood type before use, and there is a much smaller administration volume. Kcentra has a long-term history of safe and effective use outside of the U.S., especially in Europe, where it is marketed as Beriplex P/N.

Disadvantages of Kcentra include a two-and-a-half–fold greater acquisition cost vs. three-factor PCC + plasma. However, partial reimbursement may be available for Medicare patients. No head-to-head clinical data comparing Kcentra to three-factor PCC is available. Kcentra also contains heparin, thus it is not recommended for use in patients with heparin-induced thrombocytopenia (HIT). Of note, Profilnine SD does NOT contain heparin. Other limitations of Kcentra include its short stability (four hours) once reconstituted and a boxed warning regarding the risk of thromboembolic events.

Criteria for use of this agent were approved at the P&T Committee in September. An EPIC orderset is being developed to help guide safe prescribing. Dosing of Kcentra differs from three-factor PCC because it is based on baseline INR at presentation and the patient's body weight (not to exceed 100 kg). Repeated dosing of this product is not recommended. Vitamin K should be given concurrently. Please refer to the criteria for use or contact your liaison pharmacist if you have any questions about this product.

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NEWS & NOTES

Successful Research Day

The Department of Medicine once again this year had a successful presence at the Research Day on May 15th, 2014. About 37 percent of platform and poster presentations of fellows and residents were made by the members of the department. Of the platform presentations, **Dr**. **Alexandra Joseph** was the first place winner and **Dr. Shobha Vootukuri** received the third place prize. Among the poster presentations, **Dr. William Curban** was the fourth place winner.

Congratulations to all the participants and especially the top prize winners.

Department of Medicine Faculty Promotions

We are pleased to announce the promotion of two members of the Department of Medicine, effective July 1, 2014. These promotions recognize their valuable contributions to the University of Florida, the College of Medicine – Jacksonville, UF Health Jacksonville, their profession, the state of Florida and the nation. Please help me congratulate these individuals as we look forward to their future achievements in higher education.

Promotion to Associate Professor:

Dr. Ghania Masri, Divison of General Internal Medicine
Dr. Mae Sheikh-Ali, Division of Endocrinology, Diabetes and Metabolism

Please join us in congratulating Drs. Masri and Sheikh-Ali on their success.