Athens Kidney Center
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THE MONEY IS ON STOPP NOT BEERS

Aging, co-morbidity and aggressive medical care are major drivers of polypharmacy. The Beers criteria was designed to identify potentially inappropriate medications and hopefully avoid adverse drug interactions. However, the correlation between theoretical threat based on Beers criteria and actual clinical impact (based on pharmacologic morbidity) is often tenuous. A prospective study by Hamilton et al, *Arch Intern Med*, 2011, studied drug-related adversity using both Beers and STOPP (Screening Tool of Older persons' Potentially inappropriate Prescriptions) criteria in 600 consecutive hospitalizations. Adverse drug events were noted in 26% of patients, with 67% being contributory or causal to hospitalization, and 69% of those adverse drug events being potentially avoidable. Notably, prescribing against Beers guidelines only marginally influenced serious adverse drug events (odds ratio 1.27) whilst STOPP criteria was associated with a significant increase in adverse drug effects (odds ratio 1.85).

ANOTHER APPROACH TO ANEMIA MANAGEMENT IN KIDNEY FAILURE

Parenteral erythropoietin (EPO) administration has been the standard of care for chronic anemia management in renal failure. Therapy was based on the assumption that synthesis of EPO was renal-dependent and virtually lost with end-stage kidney failure. EPO synthesis and regulation in healthy individuals is controlled by oxygen-dependent hypoxia-inducible transcription factor (HIF), an autocoid secreted in response to persistent tissue hypoxemia. An experimental drug FG-2216, an orally-active prolyl-hydroxylase inhibitor acts to stabilize HIF, and phase I trials show its effectiveness in stimulating erythropoiesis in anephric individuals by reclaiming liver synthesis of EPO (Bernhardt et al, *J Am Soc Nephrol,* 2010). So far, no adverse effects have been noted with this new drug, but it is still early days.....

SEQUENCING THE CARDIO-RENAL AXIS

Heart failure, at least in Caucasian populations, has a strong heritable component. In a study by Cappola et al, *Proc Natl Acad Sci (USA)* 2011, a variant allele of the CLCNKA gene which encodes the renal chloride channel was found to significantly influence the predisposition to heart failure. It appears that reduced transmembrane chloride transport (and urinary excretion) may be part of the Holy Grail of cardio-renal syndrome, where cardiac dysfunction is intimately linked to renal dysfunction. It remains to be seen whether biological manipulation of this axis (perhaps, by stimulating chloride co-transportation or through more "distal" effects, such as altering renin-aldosterone response) could prevent future cardiac dysfunction.

DEALING WITH LATENT TUBERCULOSIS

Latent tuberculosis is not uncommon amongst certain otherwise-healthy demographic groups (e.g. recent immigrants from endemic zones), but carries a risk of progression to active tuberculosis under the "right" circumstances, such as renal failure/acute ill health or incidental immunosuppression. The tuberculin skin test (PPD) has long been a staple in the diagnosis of latent tuberculosis, where skin reaction to purified protein (tuberculin) derivative is measured as reflecting cellular immunity to previous tuberculin challenge. Unfortunately, PPD is unable to distinguish between current (active) infection and resolved (treated or latent) infection, and is subject to both human error (in interpretation of measured skin induration) and logistical error (as it requires 2 separate visits 48-72 hours apart, for administration of antigen and assessment of dermal reaction), besides being falsely negative (low sensitivity) in immunocompromised/malnourished states and being falsely positive (low specificity) as it shows cross-reactivity to non-tuberculous Mycobacteria as well as a "booster" weakly-positive reaction to previous antigenic exposure from BCG vaccination or prior PPD placement. A newer in vitro test, Interferon Gamma-Release Assay, overcomes those problems at higher cost but greater specificity for M. tuberculosis. In this test, sensitized T-cells release gamma-IF on exposure to M. tuberculosis-specific antigens, with precise laboratory measurement of such interferons (or IF-secreting T-cells). Generally, a positive PPD test and negative IF-gamma release assay suggests prior BCG vaccination, whilst the converse is commonly found in the immunocompromised. Choice of treatment is daily isoniazid x 6 months (or if "directly-observed", twice-weekly at higher doses x 6 months) vs. daily rifampin x 4 months.

DEATH & COGNITIVE DECLINE WITH ANTI-CHOLINERGIC AGENTS

Fox et al, *J Am Geriatr Soc,* 2011, studied the link between anti-cholinergic drug burden and cognitive function (based on the mini-mental state examination) over a 2 year period in over 13,000 elderly subjects. Even after adjusting for age, gender, medical co-morbidity and cognitive function at baseline, anti-cholinergic burden was associated with greater declines in cognitive function amongst study subjects. Strikingly, anti-cholinergic burden was also associated with higher mortality amongst study subjects. Just as a reminder, those anti-cholinergic drugs include anti-histamines, anti-diarrheals, anti-psychotics, anti-vertigo drugs, anti-depressants and several drugs used in treating urinary incontinence (such as Oxybutynin), peptic ulcers (such as Ranitidine/Zantac), parkinsonism (such as Amantadine) and COPD (such as Ipatropium).

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SECOND OPINION

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FROM THE EDITOR

Suicide amongst physicians is not a topic for polite conversation- at least, not around doctors, it would seem. The anomalously high incidence of completed suicides amongst our peers is the highest rate amongst any professional cadre. The reasons for this bizarre distinction are unclear, but clues abound: we are custodians of a largely male and preposterously macho subculture, where 80-hour workweeks and endless call cycles fomented during residency training, are wistfully recounted by old-timers, and worn as veritable badges of honor. Tales from those earliest renditions of unearned but unredemptive suffering are seen as character-building, not as the doctrinaire abuse of house staff it really represents. We are high achievers, beholden to a molten image of unattainable excellence, amply characterized by the "triple threat" of astute clinician, discerning scientist and spellbinding teacher of medical myth. We place huge stock on our professional standing, perpetually advancing our stock at the expense of living life. We presume on the unrequited love of those whom we are called upon to heal, and are devastated when that uneven relationship goes awry. We labor mightily under an illusion of judgment.

As high performance expectations breed performance anxiety, ironically, it is the best of us who are most afflicted by the scourge of inadequacy. The sum total of all our worst fears are realised at the first hint of a malpractice lawsuit. Contributory factors include work-related problems exacerbated by our competitive spirit (which was why we thrived in medical school, in the first place); an ever-expanding nexus of clinical responsibility; unresolved issues of intimacy and kinship, as the unyielding quest for excellence often relegates meaningful contact to a distant afterthought, and of course, financial problems, which have increasingly become a sore point with practitioners, what with the projected 29.5% pay cut come January! Our singular training in the trenches of hospital warfare was designed to erase any residua of empathy and "internalization" within, making psychic automatons of us all. This was facilitated by the insufferable blight of sleep deprivation and poor role models in senior physicians. We perfected an Olympian mien, an impenetrable veneer of impersonality and practiced condescension, handed down through generations of mentored dysfunction. We recreated both bad medicine and bad civics: making for neither good physicians nor good citizens. Whatever it took, society- and England- expected us to keep a stiff upper lip.

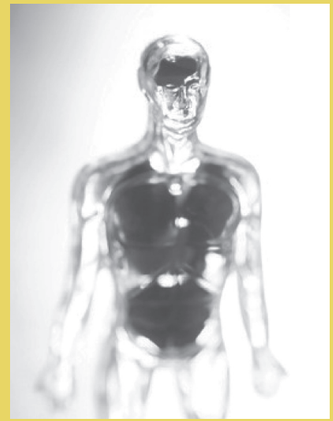
It is in that abyss of despair that we have created our own personal drama of self-destruction, first fleeing into drudgery, desperation or drugs, and when all fails, enacting the drama of suicide. And we risk widening that vortex by our complicit silence. As we avert our collective gaze from this tragedy of self-inflicted death, we all lend tacit support to its practice. Just as we sidestep the impaired physician whose skills have been laid waste by jingo and junk, we have refused to be drawn into any uncomfortable assay on peer suicide. It is therefore unsurprising that suicide rates amongst physicians have risen with each successive generation, and at present, 1 physician on average dies in this country by his or her own hands each day. Shockingly enough, even that sobering statistic is probably an underestimate. Could you imagine the societal outrage if a fully-laden Boeing aircraft, packed with physicians, were to fall out of the skies each year?

Physician suicide, unlike suicides amongst other demographic groups, does not show gender bias: a female doctor is as likely to end her own life as her male peer, and either sex has over 150% the average population risk for self-inflicted harm. Perhaps as a reflection of our training in pharmacology, we are more likely to choose self-poisoning, and are much more consistently successful at it, often completing the arc of suicide. Doctors, apparently, don't do parasuicide.

But it need not be so. We can end this conspiracy of silence. We can choose not to overlook the obvious signs of stress in each other, stop whitewashing the sepulchre of slow implosion. We can readily identify those physicians at risk, and provide timely care to our brothers-in-arms. When was the last time you saw a truly happy- joyous- physician? More radically, we can stop indoctrinating new physicians with our own sad example of perpetual busyness, poor insight and arching cynicism which only condemns them to a career of slow disillusionment at the gristmill of daily practice. We do not need another generation of innocence and idealism sacrificed at the altar of efficiency. We surely do not need another generation in tasseled loafers and outrageous mortgage payments, wistfully pining for the Good Old Days that never were.

I'll see you Friday lunch-time, at the CME lounge.

Beze Adogu, MD, Ph.D, FACP



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ZINC LOZENGES FOR COMMON COLD: IT IS THE DOSE, STUPID

Reprising the "It is the economy, stupid" mantra of Bill Clinton's improbable 1992 run for the presidency, Hemila et al, *Open Respir Med J*, 2011, pooled previous zinc-treatment trials for a meta-analysis of common cold therapy. If at least 75 mg of zinc acetate was used daily, the duration of cold symptoms was reduced by 20-42%, whilst using less than 75 mg daily was typically ineffective. Unfortunately, most commercial preparations of zinc salt either come in very low (and ineffective) doses or contain anions (such as citrate) that bind the divalent zinc cation, rendering it ineffective.

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ADVANCES IN SEPSIS MANAGEMENT

Sepsis has remained 1 of the proverbial "horsemen of death" from infectious disease. Mortality ranges from 10% to 50% depending on its clinical severity. As in all ICU cases, survival depends on accurate diagnosis, prompt treatment and prevention of complications. Positive identification of bacterial sepsis is clinical: serum procalcitonin has proven to be poorly discriminant (Tang et al, *Lancet Infect Dis*, 2007) but increase in plasma TREM-1 levels is promising (Gibot et al, *Crit Care Med*, 2005).

1. Protect airways, supplement oxygen (if needed), establish vascular access, maintain adequate (peripheral) perfusion.

2. Monitor: chest films (for acute lung injury/ARDS), blood gases (for respiratory failure/acid-base changes), urine output (for visceral perfusion/kidney damage), vital signs, blood pressure (for peripheral perfusion), mental status.

3. Restore effective circulatory volume as quickly as possible using IV fluids in discrete 500 mL boluses: aim for a mean arterial blood pressure >65 mmHg or central venous pressure of 8-12 mmHg or urine output >0.5 mL/kg/hr or mixed venous oxyhemoglobin concentration >70% or lactate clearance >10% whilst avoiding the complication of non-cardiogenic pulmonary edema (stop IV fluids once there is no further clinical improvement with boluses or with attainment of hemodynamic targets). Choice of IV fluid includes colloids (5% albumin, pentastarch) and crystalloids (isotonic saline, half-normal saline, lactated Ringer's solution): the SAFE trial (Finfer et al, N Engl J Med, 2004) did not show any important difference between colloids/crystalloids, but VISEP trial suggested a higher late mortality with pentastarch (Brunkhorst et al, N Engl J Med, 2008). Only where IV fluids are ineffective (persistent hypotension or development of non-cardiogenic pulmonary edema) should vasopressors be used (norepinephrine is "drug of choice", but may substitute dobutamine/amrinone for systolic cardiac failure as primary deficit, phenylephrine to avoid beta-adrenergic excess manifest as either tachycardia or myocardial stiffness) or early blood transfusion considered to keep hematocrit >30%.

4. Commence appropriate antibiotic treatment as quickly as possible: identify the logical/probable source/focus of infection, establish usual microbial causes, select most likely antibiotic coverage. If in doubt, obtain appropriate cultures and cover with "broad-spectrum" anti-microbials. Remove all sequestered sources of infection, including abscesses, foreign bodies, necrotic tissue. Choose the most effective and least toxic regimen: beware of the immunocompromised (neutropenic) patient and virulent (pseudomonal) microbe.

5. Ancillary care: aggressive glycemic control, nutritional supplementation, steroid boluses (in selected cases), recombinant activated Protein C (in selected cases), isolation/barrier nursing (in selected cases), ongoing drug(s) audit, monitor for adverse drug reactions/transfusion reactions, surgical drainage of abscesses, debridement of necrotic tissue.

DUALIZING ANTI-PLATELET DRUGS: WHEN & HOW?

Anti-platelet therapy in coronary artery disease is well established for both Aspirin and Plavix (Plavix, a thienopyridine pro-drug, is a suitable option for patients allergic or intolerant of ASA, as shown in the CAPRIE trial, *Lancet*, 1996). Dual anti-platelet drug treatment with both ASA and Plavix is indicated for specific acute coronary conditions and not for chronic/stable coronary artery disease as demonstrated by the CHARISMA trial (Bhatt et al, *N Engl J Med*, 2006). In these 3 clinical conditions, dual ASA-Plavix treatment is accepted except where the risk of serious bleeding trumps the benefit of extended fibrinolysis/maintained coronary artery patency: (1) ST-segment elevation MI as initial treatment (lasting 1-2 weeks) regardless of later attempts at thrombolysis/reperfusion therapy, using a loading dose of 300 mg Plavix before starting 75 mg daily doses per CLARITY-TIMI 28 trial (Sabatine et al, *N Engl J Med*, 2005) or without an initial initial loading dose per COMMIT trial (Chen et al, *Lancet*, 2005); (2) non-ST-segment elevation ACS (including unstable angina) for 3 months to 1 year as shown in CURE trial (Yusuf et al, *N Engl J Med*, 2001); (3) PTCA with stent placement used together with ASA for at least 1 month (preferably 1 year) in bare-metal stents in PCI-CURE (Mehta et al, *Lancet*, 2001) and for at least 1 year (preferably indefinitely) in drug-eluting stents (Mauri et al, *N Engl J Med*, 2007).

PHEOCHROMOCYTOMA: MYTHS & ERRORS

Pheochromocytoma are clinically rare: it is more common in autopsies (0.05%), junior resident diagnoses (frequent) and "Ground Rounds" (several) than in clinical practice (less than 0.2% in culled tertiary hospital cases of "refractory" hypertension). Clinical symptoms include the classic triad of headache (most common symptom in 65-90% of cases), sweating attacks (55-75%) and palpitations (50-70%), but other common symptoms include panic/anxiety, hypertension, pallor, extreme fatigue, weight loss, nausea and hyperglycemia. Now to correct some myths:

1. Sustained hypertension is 2x more common than paroxysmal hypertension in pheochromocytoma.

2. Normotension or even hypotension can occur with large tumors (where catecholamines are catabolized prior to secretion/release) and epinephrine-secreting tumors and following cardiac failure (arising from catecholamine-associated cardiomyopathy).

3. Incidence of orthostatic hypotension is about the same as incidence of paroxysmal hypertension (30%).

4. Biochemical screening should use a test of high sensitivity: only 2 tests have >95% sensitivity (plasma free metanephrines & urine fractionated metanephrines) but "positive" assay results should be limited to 2x upper limit of normal.

5. Clinical diagnosis should be confirmed with a test of high specificity: only 2 tests have specificity >95%: vanillylmandelic acid & urine total metanephrines.

6. Associated with hereditary syndromes: neurofibromatosis type 1 (not type 2), multiple endocrine neoplasia type 2 (not type 1), vonHippel-Lindau syndrome and paraganglioma mutations (of succinate dehydrogenase enzyme).

7. Biochemical diagnosis must always precede anatomical localization: no CT/MRI until diagnosis has been made, and where CT/MRI does not locate lesion, a "functional scan" with I131-MIBG scan is indicated.

8. Rule of 10s: 10% familial (actually higher), 10% pediatric onset, 10% with low or normal blood pressures (actually up to 40%), 10% bilateral, 10% malignant (histologically similar to non-malignant tumors, but manifests either local invasion or distant metastases, and typically have minimal inhibin/activin beta-B expression), 10% extra-adrenal, 10% calcified, 10% multiple, 10% recurrence post-surgery (valid for sporadic cases, but actually 3x that for familial syndromes), block alpha-adrenergic receptor (using prazosin, terazosin or phenoxybenzamine; if intolerant of alpha-blockers, consider calcium channel blockers or metyrosine) for 10 days before adding beta-blocker (which is indicated for those with cardiac arrhythmias) prior to surgery.

DIAGNOSIS OF SUDDEN SPELLS

Spells, sometimes referred to as Queer Turns, are short-lived, recurrent, self-limited, often stereotypical clinical symptoms that commonly defy diagnosis. The key to diagnosis lies in careful history-taking, and the physician has to decide early on whether the description reflects a neurologic (seizure-like) or hemodynamic (syncopal) event. However, the diagnostic considerations are legion and include:

1. Hyperadrenergic surges: from sympathomimetic drug intake (e.g. cocaine use, beta-agonist bronchodilator inhalation, tyramine reaction with MAOIs), pheochromocytoma.
2. Dysautonomia from spinal cord disease, Guillain-Barre syndrome, parkinsonism-plus syndromes.
3. Drug withdrawal, including delirium tremens in alcoholics, post-dialysis syndrome.
4. Panic or anxiety attacks.
5. Thyrotoxicosis.
6. Carcinoid syndrome/systemic mastocytosis, peri-menopausal syndrome/gonadal failure, idiopathic flushing disorder
7. Autonomic seizures (diencephalic epilepsy), TIAs, migraine
8. paroxysmal tachycardia syndromes including atrial fibrillation, postural orthostatic tachycardia syndrome (POTS)
9. Hypoglycemia, both fasting and reactive, including pancreatic islet cell tumors.

GALECTIN-3 AS PROGNOSTICATOR IN CARDIAC FAILURE

Galectin-3 has been long implicated as a mediator of scarring/fibrosis and remodeling in the heart and kidneys. Indeed, high plasma levels of galectin-3 are closely linked to worsened all-cause mortality as well as cardio-renal syndrome in the DEAL-HF trial (Lok et al, *Clin Res Cardiol*, 2010). A new study by Tang et al, *Am J Cardiol*, 2011, further clarifies the role of galectin-3: high plasma levels were linked to poor survival in chronic systolic heart failure but levels did not correlate with hemodynamic or echocardraphic indices, suggesting that outcomes may not necessarily be mediated through the direct (fibroblast activating) effects of galectin-3 on the heart.

OBESITY IS OBESITY, PEARS ARE AS BAD AS APPLES

Conventional wisdom held that central (apple-shaped) obesity was worse than general (pear-shaped) obesity with respects to cardiac outcomes. Hence, the insistence on hip-waist ratio measurements in Europe. Not so, asserts the Emerging Risk Factors Collaboration, *Lancet* 2011, based on a study of 221,934 subjects in 17 countries who had participated in 58 studies over more than a decade. Obesity was uniformly disadvantageous, regardless of its pedigree or phenotypic expression, but interestingly, obesity did not provide further prognostic weight in individuals where the presence of diabetes mellitus, serum lipid levels and history of arterial hypertension were already accounted for. Looks like our European brothers won't have to measure hip/waist ratios any longer, but BMI measurements might still linger as an "early warning device" for cardiac risk.

NASAL CARRIAGE OF MRSA: IS HOT BEVERAGE DRINKING THE ANSWER?

Matheson et al, *Ann Fam Med*, 2011, report that MRSA nasal colonization was less common amongst those who drank hot tea and/or coffee. Using the NHANES data-base, the researchers from Charleston, SC, found that hot beverage consumption reduced the risk of nasal carriage by 47%, even after adjusting for race, gender, sex, socio-economic status, antibiotic use and health/hospitalization history. Sadly, this protection did not extend to drinkers of soda beverages or iced tea. And no, the stock prices for Maxwell House has not gone up yet.

DISTINGUISHING CYSTITIS (LOWER URINARY TRACT INFECTION) FROM PYELONEPHRITIS

1. Presence of fever >38.5 degrees F, flank pain, prominent gastro-intestinal symptoms (nausea and vomiting), rigors and costo-vertebral angle percussion tenderness favor pyelonephritis; however, a third of pyelonephritis will not have those "distinguishing" findings, and a sixth of acute cystitis cases will.

2. Presence of WBC casts in stained urine sediment (found in 30% of pyelonephritis).

3. Peripheral leucocytosis is found in three-quarters of pyelonephritis cases, often with left-ward shift (immature forms, notably bands).

4. Positive blood cultures (only in 20% of pyelonephritis, though half of those might quickly deteriorate, going into septic shock).

5. Other suggestive findings include elevated C-reactive peptide (this is a simple, effective screening test: if not elevated, it effectively excludes pyelonephritis), elevated LDH4/LDH5 isozymes, proteinuria >300 mg/day, failure to excrete contrast dye on IVP, decreased urine concentration ability (despite signs of dehydration/hypovolemia, urine specific gravity of <1.015, sometimes with isosthenuria at 1.010), increased renal uptake of 67-gallium isotope on scintigram, large-sized kidneys (nephromegaly) on ultrasound.

6. Failure of infection to respond to one-time oral antibiotic regime.

7. Research studies utilize a positive Fairley test (rise in urinary bladder colony count >10% above baseline following serial antibiotic solution bladder irrigation x 45 minutes and saline irrigation x 100 mL) or positive Stamey test (direct ureteral catheterization demonstrating bacterial growth in urine samples, but false positives common in vesico-ureteral reflux disease) or positive antibody-coated urinary bacteria (as demonstrated with anti-human immunoglobulin immunofluorescent assay, but false positives common in local pelvic inflammatory disorders and ulcerative cystitis/prostatitis, whilst false negative results occur if pyelonephritis is of sudden onset prior to development of antimicrobial anti-capsid antibodies by host).

I THINK WE ALWAYS SUSPECTED THIS

From the hallowed precincts of our teaching hospitals comes another addition to the public lexicon: the July Effect joins past notables, such as the November Surprise (Lee Atwater, I presume), the May Bumps (Cambridge, anyone?), the August Break (of tropical climatology), et cetera. With each transition at the close of the academic year, new residents replace experienced, weather-beaten old-timers on the wards. A systematic review of this phenomenon by Young et al, *Ann Intern Med*, 2011, reveals that such transitions lead to higher in-patient mortality, decreased efficiency and increased length of stay at our teaching hospitals. Perhaps, we shouldn't graduate all our senior residents on the same day in July.....