Athens Kidney Center
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RETURN SERVICE REQUESTED

BEWARE OF DRUGS (IN YOUNG WOMEN)

Medications are commonly prescribed as part of most clinical interventions. In treating women of child-bearing age, it is cautionary to consider any possible teratogenic effects of prescribed medicines. This is even more important whilst treating diseases that are more prevalent within that demographic. A new study highlights the teratogenic potential of nitrofurantoin and sulfonamides, both commonly prescribed antibiotics for UTI (Crider et al, *Arch Pediatr Adolesc Med*, 2009). Added to the well-known risks of hemolysis in G6PD-deficient patients using nitrofurantoin, kernicterus in neonates exposed to sulfonamides, and now teratogenicity (anophthalmia with nitrofurantoin, anencephaly with sulfonamides, and more weakly, associationships between transverse limb defects for erythromycin, intercalary limb deficiency for penicillins, atrial septal defects for cephalosporins) all antibiotic use in pregnancy must be closely monitored.

THROMBOLYSIS IN ELDERLY STROKE VICTIMS: FULL STEAM AHEAD

Institutional (and personal) bias weighs heavily against the elderly: being under-represented in most clinical trials, physicians often do not know whether guidelines equally apply to our senior citizens. Fortunately, that wall is beginning to crumble. We know from the PROGRESS trial that long-term prognosis following acute ischemic strokes is linked to BP control, yet tight control of hypertension in the elderly was inconsistent, until the data from HYVET was published (Beckett et al, *N England J Med*, 2008). Similarly, thrombolytics such as recombinant tissue plasminogen activator (alteplase) are rarely used in elderly stroke patients, despite a body of information indicating that those drugs are indeed safe in the over-80s (Engelter et al, *Age Ageing*, 2006; Toni et al, *Cerebrovasc Dis*, 2008; Berrouschot et al, *Stroke*, 2005). Now, Mishra et al, *BMJ*, 2010, compare outcomes in elderly stroke patients with similar baseline stroke severity who received IV thrombolytics versus those who did not. Functional outcomes as measured by Rankin scores were superior at 3 months amongst those who received thrombolytics, and equivalent to improved outcomes amongst younger peers. Another barrier erected on the altar of subjective bias crumbles.....

KIDNEY TRANSPLANTATION IN HIV

ESRD afflicts HIV-positive and HIV-negative alike; only a quarter of ESRD in HIV-positive patients are due to HIV-related nephropathy, others largely reflecting causality in the general population. Transplantation in HIV-positive recipients has been controversial. Now comes a paper culled from 19 transplant centers showing that with careful selection, ESRD patients with stable, treated HIV and low/undetectable circulating HIV RNA titers are good transplant candidates (Stock et al, *N England J Medicine*, 2010). HIV-positive patients had more frequent acute allograft rejection episodes, but HIV did not progress post-transplantation despite addition of immunosuppressive drugs. The biggest challenge was negotiating drug-drug interactions between HAART and immunosuppressive cocktails. Both patient and allograft survival were comparable to national rates reported in HIV-negative transplant recipients.

CPAP FOR HYPERTENSION?

Obstructive sleep apnea is a recognized risk factor for systemic (and pulmonary) hypertension. A multi-center, prospective, double-blind, placebo-controlled, randomized study from Spain suggests that 3 months of CPAP had a modest effect in reducing ambulatory blood pressures in men with obstructive sleep apnea (Duran-Cantolla et al, *BMJ*, 2010).

FASCINOMA OF THE MONTH: MYOSITIS OSSIFICANS

There are 2 distinct types: (1) acquired MO following deep-tissue (muscle) trauma, around immobilized lower limb joints in paraplegics/hip replacement surgery, and within hematomas in hemophiliacs; (2) hereditary (progressive) MO which is an autosomal dominant condition with variable expressivity/penetrance associated with digital skeletal abnormalities (of hands/feet) and recurrent attacks of painful soft tissue swelling, followed by secondary ectopic (heterotopic) bone formation. In both conditions, true bone is laid down, not calcium phosphate or hydroxyapatite. The bony accretions may be discrete or attached to other bony structures. Histologic differentiation from osteosarcoma on biopsy is difficult, but true osteosarcoma can also very rarely form within the bone matrix of MO. Hereditary MO is suspected from short thumbs/big toes at birth, short/fused phalanges, episodes of soft tissue swellings precipitated by trauma/injury in childhood, and radiologic evidence of ectopic bone formation. Later in life, bone deformities and axial skeletal rigidity is noted, with the neck, shoulders, chest wall being first involved, involving the lower limbs only later in adulthood. There is no treatment.

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SECOND OPINION

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FROM THE EDITOR

Welcome, 2011. Glad to finally meet you.

As with each new year, 2011 brings a promise of new insights, offers new tidings of hope, and creates new opportunities. Old and familiar things are made new once more, as we are offered another chance at redemption. Being an eternal optimist, I celebrate the New Year illusion of rebirth.

For most physicians, the last year was eventful on many fronts: scientific breakthroughs, new therapeutic remedies, old battles and fraught alliances renewed against disease and pestilence. We were eye-witnesses to the social upheaval wrought by the economic collapse of 2009, professional anxiety engendered by threats of health care overhaul, Main Street angst at Wall Street recidivism, and not least, Tea Party politics. Personally, I prefer coffee.

Abroad, there has been some good news to cheer the weary doctor at the HIV front: the United Nations Agency on AIDS reports a 16% drop in new HIV infections over the last decade, anti-retroviral drugs were able to halve new HIV infections across 6 countries amongst men who have sex with men, and in a startling break from long-established ecclesiastical tradition, Pope Benedict XVI recently appeared to endorse condom use. For sure, the endorsement was characteristically nuanced and suitably tepid; indeed it was a ringing non-endorsing endorsement. But little matter: theological victories are measured in little steps. Today, condoms; tomorrow, contraception- or perhaps, even sanctioning sex outside marriage, a stricture which has not succeeded in keeping randy priests off little boys.

I am constrained to remind my more skeptical brethren that ethics is a dynamic construct, and the ways of the Mother Church can be slow, insipid and confounding. Recall that in the early days of solid organ transplantation, that entire concept of "organ recycling" was anathema to the Catholic church, being forcefully denounced in the 1930 papal encyclical from Pope Pius XI. Fast-forward 50 years on, when Pope John Paul II described organ donation as "an act of supreme charity".

And it was not a peculiarly Catholic iniquity: most other religions were skeptical of organ transplantation at first. With the exception of Gypsies (Romany) who have remained a solitary pillar of atavistic literalism-thumbing their collective noses at organ donation- all other religious persuasions have slowly accepted the gift of recycled organs. Though not quite supportive yet, Jehovah's Witnesses and adherents of the Shinto faith have moved from a posture of active hostility to a studied indifference. Even Buddhists and Scientologists, in the spirit of giving Caesar what is Caesar's, have now left the life-affirming decision of organ transplantation to individual members. This gradual retreat from vicarious intercession took decades of quiet resistance and reverse-proselytism. Cynics have countered- with some measure of justification- that change was inevitable, implying that religious groups might have acted out of craven self-preservation. However, that is a dangerous misreading of history: though insistence on medieval concepts of "blood, body and soul" might decimate the ranks of the faithful, religious dogma prides itself on its resolute orthodoxy, studiously defying any breaches by either science or common sense. Indeed, no less an authority as William Ralph Inge, late Dean of St. Paul's Cathedral, London, had once memorably opined that, "a church that is married to the spirit of this age, is bound to be a widow in the next". Strange are the workings of the canonical mind.

As all religions, openly or grudgingly, look up to the Holy See for guidance, the Pope's pronouncements on all things spiritual and temporal, do matter. Therefore, the fight against AIDS, the pestilence of our age, can have no better advocate than Pope Benedict XVI. Each retreat from dogma is a minor victory for mankind, each concession represents another wretched soul saved from unspeakable horror. I care not if the retreat is insincere or self-preserving; I do not care if it represents the canonical equivalent of failing to look someone straight in the eye.

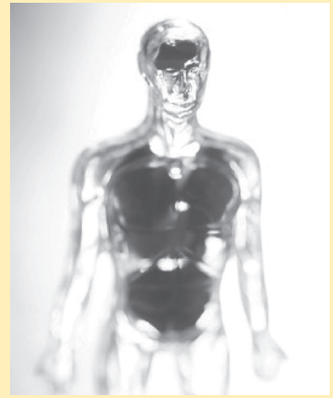
A very happy New Year to both you and yours, and may this New Year bring you more opportunities for personal fulfillment.

Goodbye, 2010. I hardly knew you.

Beze Adogu, MD, Ph.D, FACP

ATRIAL FIBRILLATION: FROM CHADS(2) TO HATCH

Paroxysmal atrial fibrillation frequently progresses into persistent atrial fibrillation. To understand the risk factors for progression, De Vos et al, *J American Coll Cardiol*, 2010, recruited 1219 patients with paroxysmal atrial fibrillation who were followed over 1 year. Fifteen (15%) percent progressed to persistent AF. Predictors of progression were: presence of Hypertension, advanced Age (greater than 75 y.o.), prior TIA or stroke, evidence of COPD, and presence of Heart failure. To calculate a HATCH score: 1 x [Hypertension] + 1 x [Age >75] + 2 x [TIA or stroke] + 1 x [COPD] + 2 x [Heart Failure]. Almost 50% of patients with a HATCH score of 5 or more progressed to persistent AF, but progression only occurred in 6% of patients with a zero HATCH score.



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FIRST, CATHETERIZE ASAP

The long-term outcomes data from the DANAMI-2 (Danish Acute Myocardial Infarction-2) trial is finally out (Nielsen et al, *Circulation*, 2010): even after 7.8 years (on average), the advantages of of mechanical reperfusion with primary PCI (percutaneous coronary intervention) a.k.a."cardiac stenting" over pharmacologic reperfusion with fibrinolytic treatment (such as heparin, heparinoids, alteplase) in ST-elevation acute MI persist. This superiority holds even for patients who have to be transported to a "tertiary" center to achieve mechanical reperfusion. Mechanical reperfusion is associated with fewer bleeding (intracranial, retinal) complications, a higher patency rate, lower rates of later re-infarction, and provides immediate "directed" treatment of the blocked artery or ruptured plaque. However, if "rescue" treatment is aggressively pursued, with rapid PCI referral and rmechanical reperfusion within 30 days after initial pharmacologic reperfusion as was the case in the CAPTIM (Comparison of primary Angioplasty and Pre-hospital fibrinolysis in Treatment of acute Myocardial Infarction) trial (Bonnefoy et al, *European Heart J*, 2009), then long-term outcomes are equivalent (or perhaps, even superior) with initial pharmacologic reperfusion treatment. Moral: if the "Big One" hits, chew an aspirin, get to a cath lab within 2 hours, or quickly start lytic treatment wherever you are.

EVIDENCE THAT OBESITY PRE-DATES BIRTH

Nobody knows what should be the optimal weight gain in pregnancy. The reasons are complex, in part because it depends on pre-pregnancy "base" weight, amniotic fluid volume, maternal blood volume expansion, maternal weight increase, fetal weight increase, placental weight, et cetera. Still, the ALSPAC study (Avon Longitudinal Study of Parents and Children) from Bristol, England, suggests that the cultural mandate to "eat for two" during pregnancy- no doubt a vestigial evolutionary remnant from aeons of famine and maternal undernutrition- risks future cardiovascular disease in children. Mothers gaining more weight in pregnancy above IOM guidelines had children, who by age 9 years were 1 kg heavier than their peers, had 2 cm larger waistlines than their peers, had 1 mmHg higher systolic blood pressures, 15% higher higher inflammatory biomarkers and 0.03 mmol/L lower HDL cholesterol levels (Fraser et al, *Circulation*, 2010).

THE END OF ADDED SALT

Anyone who has lived or visited stateside, knows how much we love salt. Bibbins-Domingo et al, *N England J Medicine*, 2010, provides compelling data that a very modest 3 g/day reduction in dietary salt intake would foster cardiovascular benefits at par with current efforts to limit tobacco use, obesity or cholesterol levels. Indeed, they calculate that salt restriction would reduce new cases of coronary heart disease by 60,000-120,000 and strokes by 32,000-66,000, adding 194,000-392,000 quality-adjusted life years to our population, whilst total all-cause mortality should drop by 44,000-92,000. For the fiscally-minded, that translates to a reduction in health-care costs by $10 billion-$24 billion. Somewhere within the vast recesses of Gracie Mansion, a light is going off in Mayor Bloomberg's brain.

ITS ALL ABOUT TIMING

Every resident knows that ICU care in the month of July, weekend hospitalizations, stroke during a public holiday and cardiac arrests after 5:00 PM often lead to worse outcomes. At those times, new residents are taking over from the old-and-tested warhorses, experienced critical care nurses are tending to their families and attending physicians are home in bed. Either way, bad things are more likely to happen. Now comes a retrospective study from Johns Hopkins confirming that avoidable surgical mistakes where more likely to occur at night: patients undergoing liver transplantation at night had a longer pre-operative time, a higher risk of early death and more (vascular) surgical complications (Lonze et al, *American J Transplantation*, 2010). Interestingly, I recall that a somewhat similar study for kidney transplantation published in 2008 had only shown minor differences on complications and allograft survival based on timing of surgery (Fechner et al, *Transplantation Proc*, 2008).

SECONDARY HYPERTENSION

The question is often asked if an atypical or poorly-controlled hypertensive has "secondary" disease. Actually, that consideration ought to be entertained for all hypertensives, as it offers the only true possibility for "clinical cure" in hypertension management. Perhaps, 1-15% of hypertension is attributable to "secondary" causation, depending on the practice setting: close to 1% in primary care, closer to 15% in tertiary referral centers. As secondary hypertension is an uncommon diagnosis, often associated with expensive confirmatory testing and uncertain prognostic advantages (from its specific diagnosis), screening for disease must be cost-effective.

1. Suspect in patients with onset of hypertension at extremes of age (under 20 y.o. and over 65 y.o.); poorly controlled hypertension (after first excluding therapeutic non-compliance); early onset of hypertension-related complications (such as kidney failure or stroke); recurrent pulmonary edema (in absence of systolic heart failure).

2. The 5 most common causes of secondary hypertension are chronic kidney disease, renal artery stenosis, primary aldosteronism, drug-related hypertension and thyroid disease. Those are the 5 you need to know, but surprisingly, everyone is on the lookout for pheochromocytoma (which you probably will never see).

3. A first-line screen should include a competent physical exam (look for signs of pregnancy, obesity, virilism, diminished arterial pulses, history of smoking, ballotable kidneys, abdominal bruit, exophthalmos, thyromegaly, hypertensive retinopathy), basic metabolic panel (hypokalemic metabolic alkalosis in a diuretic-naive patient suggests aldosteronism), ultrasensitive TSH, serum PTH (parathyroid hormone), urine/blood drug screen (catecholamine-releasing medications such as caffeine, amphetamines, cocaine, as well as adrenergic agonists, and also in certain circumstances, ergot alkaloids, disulfiram/Antabuse, MAOIs/cheese, cyclosporine, estrogens), urinalysis, renal ultrasound (search for cystic degeneration, size asymmetry >1.5 cm, cortical atrophy, obstructive disease, elevated resistive index).

4. Screening for primary aldosteronism: (a) presence of unexplained hypokalemic metabolic alkalosis, (b) serum aldosterone > 15 ng/dL, (c) aldosterone/plasma renin ratio >25, (d) daily urine K excretion >40 mmol/day in spite of hypokalemia (renal potassium wasting). To distinguish between pseudo-aldosteronic states (caused by excessive Na reabsorption via epithelial sodium channels, all other features of hyperaldosteronism are present except for the defining absence of high serum aldosterone) vs secondary aldosteronism (a high renin state from kidney disease/edema or intravascular contraction stimulates aldosterone release, therefore aldosterone/renin ratio is low) vs thin-slice CT cuts of adrenal (to detect adenomas of adrenal cortex).

ALL VANCOMYCINS ARE NOT EQUAL

Vesga et al, *Antimicrob Agents Chemother,* 2010, report from Colombia that brand-name Vancomycin consistently outperformed generics based on a clinical trial using generic drugs produced prior to 2005 in the United States, France, Argentina and Mexico. In this important study, pharmaceutical equivalence ("bio-equivalence" based on pharmacokinetic profiles in healthy volunteers) did not match therapeutic equivalence, irrespective of manufacturer, country or climate. However, since 2005, manufacturers who "made nice" with Eli Lilly & Co, have attained therapeutic equivalence by the simple expedient of tapping into Eli Lilly's intellectual know-how. Given the risk of spreading antibiotic drug resistance, isn't it time we demanded therapeutic equivalence from all generics?

GETTING TO GRIPS WITH IBS

Irritable bowel syndrome is a very common functional entity afflicting between 2-20% of most studied populations, with neither biochemical nor structural correlates, and characterized by abdominal pain plus altered bowel habits. The majority of illness remains undiagnosed, but IBS is thought to be more common amongst the young, female gender, unemployed and unmarried. Causation is multi-factorial, being ascribed to abnormal CNS-gut interactions leading to altered gut motility and visceral perception. Commonly identified triggers include GI infections, chronic stress and non-specific colitis. Abdominal pain is typically triggered by eating, relieved by defecation, and associated with bloating, altered fecal consistency and sensation of incomplete evacuation. Syndromic presentation can be predominantly with constipation (IBS-C) or diarrhea (IBS-D) or mixed (IBS-M) but it is crucial not to misdiagnose inflammatory bowel disease or colonic cancer ("red flags" for those being bloody stools, nocturnal diarrheal symptoms [nocturnal pain is not discriminatory], weight loss, anemia, positive family history of colitis/cancer, onset at age >50 y.o.). In selected cases, it may be important to exclude thyroid disease, intestinal infections/parasitoses, celiac disease (serum IgG antibodies to gliadin/transglutaminase), small intestinal bacterial overgrowth and/or lactose intolerance (by breath testing). Treatment involves psychological support, dietary manipulation (small, frequent, high-fiber meals with restricted fats, milk, caffeine and possibly fructose/gluten), tricyclic antidepressants/SSRIs, bulk-forming agents in IBS-C (psyllium 2.5-10 g p.o. QD-TID, methylcellulose 500-1000 mg p.o. TID), chloride channel activators for IBS-C (lubiprostone 8-24 mcg p.o. BID), 5-HT4 receptor agonists for IBS-C (Tegaserod 6 mg p.o. BID restricted to emergency treatment because of myocardial adversity), anti-diarrheal drugs for IBS-D (loperamide 1-8 mg p.o. QID or diphenoxylate 5 mg p.o. BID-QID are often employed but not shown to be effective for symptom control), 5-HT3 antagonists for IBS-D (Alosteron 0.5-1 mg p.o. BID is effective but risks ischemic colitis, therefore only used as emergent treatment), non-absorbable intestinal antibiotics for IBS-D (rifaximin 550 mg p.o. TID x 2 weeks), antispasmodics (such as hyoscamine 0.125 mg SL or p.o. QD-QID, dicyclomine 10-20 mg p.o. BID, clidinium 2.5 mg TID-QID which all tend to work best pre-prandially given 30 mins before meals), probiotics for excessive bloating (efficacy untested, but use of lactobacilli and bifidobacteria is common).

CHRONIC PERSISTENT INFECTIONS

Persistence of microbial infections typically result from antibiotic resistance in the acute phase, and "microbial persistence" in the chronic phase. Persistence, which defines refractory infection despite antibiotic susceptibility, is associated with the formation of a biofilm. A biofilm is a privileged "sanctuary" community of microbes embedded in layers of exopolymers, either within mechanical devices, foreign bodies or necrotic tissue. Persistence of microbes within a biofilm may be attributable in part to poor antibiotic penetration into the exopolymer bed, evasion of the host immune system, slow microbial cell growth and retarded microbial cellular metabolism. However, it appears that the most important cause is development of a unique sub-set of dormant "persister" microbes (which are phenotypically distinct but genetically identical to native microbes, neither growing nor dying on exposure to antibiotics, and are therefore not antibiotic-resistant mutants) within the biofilm. Persisters cyclically repopulate the microbial population within the biofilm. Such biologically dormant cells have inactivated the cellular targets of antibiotic action, allowing such "persisters" to escape antibiotic-associated cytotoxicity. Therefore, persisters remain viable almost indefinitely, but at the high biological price of non-propagation. The biological basis of "microbial persistence" is still unclear; current research suggests that this phenotypic switch is mediated by up-regulation of genes (which generally inhibit protein protein synthesis, either at the DNA, mRNA or peptide synthesis level, such as might occur with formation of mRNA endonucleases) that can confer biological dormancy. This is thought to be the biological explanation for "latent" tuberculosis: an estimated 33% of the population have been exposed to tuberculosis(usually through Grandma's chronic cough), and carry "latent" forms of tuberculosis, though only 2-10% of such carriers ever go on to develop "active" tuberculosis infection during their life-time.

IF YOU GOTTA JUMP, JUMP

Different practices use different loading doses of Clopidogrel (Plavix) during primary PCI for ST-segment elevation acute MI. STEMI is associated with activation of the canonical stress response as well as increased platelet reactivity. Plavix improves post-PCI outcomes through platelet inhibition and prevention of platelet-associated vascular thrombosis. Rapid and potent platelet inhibition is therefore crucial in STEMI management. New data suggests that 600 mg Plavix load is preferable to 300 mg load in PCI under those circumstances (Mangiacapra et al, *American J Cardiol*, 2010). Other studies, such as the TRITON-TIMI 38 indicate that the newer, more potent Prasugrel provides further platelet inhibition which translates to better outcomes in STEMI (Montalescot et al, *Lancet*, 2009).

DEPARTMENT OF NEW DRUGS

1. **Krystexxa (Pegloticase)**
Pegloticase is recombinant uricase protein which catalyzes the oxidation of uric acid to allantoin (a step missing in primates, for which we pay the price of gout). It is indicated only for treatment of refractory gout, either from non-responsive to allopurinol/etc or intolerance to conventional therapy. Administer as 8 mg in 250 mL of isotonic saline IV over 2-4 hours q 2 weeks, after pre-medication for infusion reactions/anaphylaxis (which occurs in >5% of all recipients).
2. **Pradaxa (Dabigatran)**
Dabigatran, the long-awaited direct thrombin inhibitor, is an oral anticoagulant indicated for prevention of thrombo-embolism in atrial fibrillation and similar conditions. Dosed at 150 mg p.o. BID (75 mg p.o. BID in advanced CKD) with no need for routine INR monitoring, this new drug promises to replace Coumadin as oral anticoagulant of choice.

REFERRAL BIAS: WHERE THE BEEF IS

A study from University College, London, UK, looks into referral patterns for post-menopausal bleeding, hip pain and dyspepsia amongst 326 general medical practices in the UK (McBride et al, *BMJ*, 2010). A majority of post-menopausal bleeders were referred, but less than 20% of those presenting with either hip pain or dyspepsia were ever referred. Overall, older patients were less likely to be referred; the "socially disadvantaged" were less likely to be referred for further care if presenting with either hip pain or dyspepsia (under age 55 y.o.); also, women were less likely to be referred for hip pain.