Athens Kidney Center
1440 North Chase Street
Athens, GA 30601

RETURN SERVICE REQUESTED

TREATING PULMONARY HYPERTENSION

Pulmonary hypertension is uncommon, clinically progressive, easily misdiagnosed, difficult to manage, and potentially fatal (with development of right heart failure). Functional capacity does not reliably correlate to survival; there are no reliable markers for long-term monitoring; cost can be crippling; and sadly, management has become extremely specialized and institution-dependent. However, without treatment, 65% of patients are dead within 5 years.

New medications have been approved for treatment, and several consensus panels are working out optimal management strategies, which are currently in flux. Current treatment is based on reducing thrombo-embolic risk, improving cardiac output, and based on the results of acute vasoreactivity test, early introduction of high-dose calcium channel blockers, a strategy that has not yet been formally approved by the FDA.

1. Level 1 treatment for comorbidities: anticoagulation with coumadin, low salt diet, diuretic treatment, magnesium supplementation (if indicated), smoking cessation, consider IVC filter placement (if indicated), oxygen supplementation as needed.
2. Level 2 treatment for cardiac failure or supraventricular arrhythmias: digoxin
3. Positive acute vasoreactivity test: start oral calcium channel blockers, preferably amlodipine (or diltiazem); recheck reactivity status q 3 months.
4. Negative vasoreactivity test: if in moderate-severe heart failure, start prostacyclin (Epoprostenol 2 ng/kg/min IV titrating upwards for clinical benefit q 15 mins, is the first choice; Ilioprost 2.5-5 mcg inhaled 5-10 times daily, titrating dose upwards for clinical benefit to a maximum of 45 mcg daily is second choice; Treprostinil 1.25 ng/kg/min titrating upwards q week for clinical benefit is third option, but can also be used as inhaled drug 18 mcg/breath at 54 mcg inhaled QID and titrated upwards for clinical benefit q weekly to maximum of 486 mcg inhaled QID)
5. Negative vasoreactivity test: if without heart failure or mild heart failure, consider phosphodiesterase-5 inhibitor: sildenafil 20 mg p.o. TID is initial option, followed later with tadalafil 40 mg p.o. QD; second-line drug option is endothelin receptor antagonist (bosentan 125-250 mg p.o. BID, then switch to ambrisentan 5-10 mg p.o. q daily)
6. In refractory/severe disease: consider combination drug therapy

the SECOND OPINION

July 2010 | *A monthly medical newsletter for the Athens medical community* | Volume 1, #7

FROM THE EDITOR

Pity those unsung folks who have to come up with consensus treatment guidelines. The need (for therapeutic guidance) is often urgent, the supporting data is seldom explicit, the end-user physicians are generally skeptical, drug companies are overly intrusive, the pay for your effort is negligible, and all you get in return is the opportunity to rewrite the whole thing as new information erupts, even before the ink is dry on the first published draft. Perhaps nothing illustrates this spectacle better than the guidelines created by KDOQI on anemia management for the nephrology community, before that singular effort dissolved in recriminations and endless controversy. The alleged ties of some co-panelists to either Amgen or OrthoBiotech- both being financially interested parties to the conclusions and recommendations being debated- tell some, but not all the story. The shifting sands of science, changing interpretations of relevant data, outrage over perceived professional breaches, over-the-top obloquy leveled against key panelists have all contributed to the serial revisitations of KDOQI guidelines ever since. What we now have is a rootless palimpsest, lacking both authority and conviction.

I have also followed the tentative steps by the Pulmonary community to evolve workable guidelines in treating pulmonary hypertension, which I have tried to summarize in this edition. Ditto for the competing (and ever-changing) recipes in titrating immuno-suppressant drugs following solid organ transplantation. As a younger Joan Rivers once memorably opined: "The trouble with housework is that it is boring and repetitive; you make the bed, do the dishes, and six months later you have to start all over again". Therein lies the angst of the true domestic- or consensus panelist.

Once upon a medical residency ago, I watched from a privileged front-row seat as treatment guidelines were being put together. It was not a particularly pretty sight. By its very nature, as well as the tentativeness of all new science, you would imagine that those efforts ought to be paeans to compromise, amity and an abiding sense of obedience to scientific norms. In reality, the final product is often the end-result of capitulation, obeisance and mutual antipathy: he who shouts loudest, wins. After such close encounters, like the lady of Shalott, you could never be able to look any guideline straight in the face.

Those are not isolated instances. The recidivist nature of our "winner takes all" culture assures that any successful imposition on such panels would certainly repeat itself. Little wonder that our dearly beloved academic community is slowly beginning to look like a fractious cult, where each intellectual (overlord) has a committed following (herd), and where the raw, festering animosity borne from differences in scientific perspective is of such feral intensity, that it can only exist otherwise within a luckless marriage.

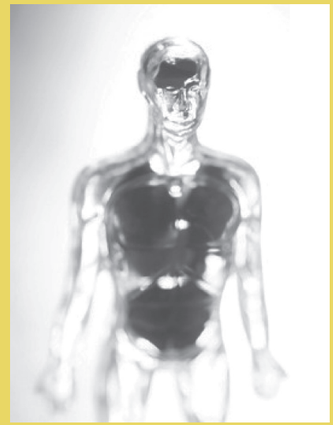
The uproar that greeted the KDOQI debacle is now stale news. I do not intend to revisit the details of that unfortunate blot on the renal community in this newsletter. However, as clinicians, we must always be careful to purge ourselves of any real or implied conflicts of interest. That is the only way to maintain the integrity of a very important clinical process: that of formulating guidelines, trying to make sense of data, even before the smoke of uncertainty has cleared. Blithely dismissing the concerns of the silent majority of clinicians that such conflicts of interest are ultimately harmful to the process, its product, and the purveyors of same, is simply wrong-headed. It is not that intellectuals cannot be trusted to come up with unbiased guidelines, but the incestuous relationship between industry and science has verily tainted the drinking well for all. I have never subscribed to the "everybody has a price" philosophy, but when burdened with such an onerous task, it is the duty- and privilege- of the chosen to demonstrate that s/he is incorruptible. Except, of course, you happen to be Caesar's wife.

See you Friday lunch-time, at the CME lounge.

Beze Adogu, MD, Ph.D, FACP

THE END OF FRAMINGHAM?

Clinical prediction of cardiovascular risk has relied on the well-tested Framingham risk score (i.e. advanced age, male sex, history of smoking, systolic BP and serum lipid levels), which has been extrapolated to all parts of the world, despite the fact that this model was based on a middle-class, mostly Caucasian, New England population derived on dated health indices which are about 40 years old. Now comes the contender to the throne of CVS risk factors: Q Risk 2 (Hippisley-Cox et al, *British Med J*, 2008) which is a "souped up", that is, Framingham-on-steroids, but with a decidedly British accent. It is based on both traditional CVS risk factors plus new considerations such as family history of CVS disease, BMI, social class, ethnicity/race, presence of atrial fibrillation, history of hypertension, presence of CKD, history of diabetes mellitus and history of rheumatoid arthritis. Now, the real work begins to validate this new score system outside Her Majesty's domains.



Contents Within:

Athens Kidney Center
1440 North Chase St • Athens, GA 30601
706-227-2110 (p)
706-227-2116 (f)
www.athenskidneycenter.com

NEW DRUG HIGHLIGHT

FDA has approved IV ibuprofen (Caldolor) used at 400-800 mg boluses q 6 hrs (each bolus administered over 30 minutes) for treatment of moderate pain, either alone or as an adjunct to opiates. It promises to be an instant favorite in the emergency department as well as the surgical floor, both as an analgesic and an anti-pyretic. It also promises to add to the not-insignificant nephrotoxicity (and gastrotoxicity) of NSAIDs as witnessed with IV ketorolac (Toradol). Safety data are still emerging, but I would suggest that for patients at higher renal risk (dehydrated, oliguric, history of CKD, hypotensive, recent nephrotoxic exposure) the following guidelines might help: use lower (400 mg) dose; extend infusion time over 1 hour; administer with at least 500 mL of IV fluid; do not co-administer with ACE inhibitors/ARBs; avoid in acute coronary syndrome; avoid if recent spike in serum creatinine; avoid in those with platelet dysfunction or active bleeding; do not give concurrently with IV contrast dye or nephrotoxic antibiotics (such as aminoglycosides).

VANCOMYCIN NEPHROTOXICITY

The renal safety of the glycopeptide antibiotic, vancomycin, has been fiercely debated, with purists insisting that newer formulations of the drug may not be nephrotoxic (Hazlewood et al, *Am J Medicine*, 2010). That contention flies in the face of clinical experience: most clinicians agree that vancomycin is acutely nephrotoxic (Frimat et al, *Nephrol Dial Transplantation*, 1985) either through direct tubulotoxicity as a consequence of oxidative stress or acute (granulomatous) interstitial nephritis. To minimize vancomycin-associated nephrotoxicity, I will reiterate the guiding principles of treatment:

1. Vancomycin treatment is not superior to penicillins for methicillin-sensitive gram positive cocci.
2. Drug elimination half-life is 4-6 hours, but in anephric patients (on dialysis) rises to a mean of 7.5 days; even non-renal excretion pathways which ordinarily account for ~30% of drug elimination declines in anephric patients to under 5 mL/day.
3. Retained serum toxins in uremia can be falsely detected as "vancomycin" in drug assays thereby spuriously elevating serum drug levels in CKD patients.
4. Risk factors for nephrotoxicity include: increased body weight, prior CKD, history of chronic liver disease, drug dose >4 g/day, initiation of drug therapy in ICU setting, advanced age, concurrent use of aminoglycosides or loop diuretics, history of clinical hypertension (Lodise et al, *Antimicrob Agents Chemother*, 2008).
5. Vancomycin-related nephrotoxicity is potentially reversible, if detected early, and drug is withdrawn.
6. Peak serum levels have no clinical utility in predicting either efficacy or toxicity.
7. Trough serum concentrations reflecting "steady state" drug levels prior to the next drug administration accurately predict drug efficacy but do not necessarily predict tissue/organ toxicity (most specifically, the data suggests that serum levels do not correlate with ototoxicity, and not reliably for nephrotoxicity).
8. Trough levels >10 mg/L are demonstrably effective for Staph aureus infections, and superior treatment results are obtainable for tissue-invasive infections at trough levels of 15-20 mg/L; long-term organ safety at those levels is uncertain.
9. Based on presumed pathogenesis of vancomycin-induced oxidative stress in rat models, anti-oxidants such as Procrit (Cetin et al, *Clin Experimental Pharmacol Physiol*, 2007), vitamin C, vitamin E, Mucomyst, et cetera, appear to reverse renal damage.

PREVENTING DIABETIC NEPHROPATHY

Diabetic nephropathy is the most common cause of chronic kidney failure in the United States. Development of nephropathy in diabetics is dependent on multiple familial/genetic factors, degree of hyperglycemia, and susceptibility to oxidative stress, mediated through pro-inflammatory and fibrogenetic autocoids, including the renin-angiotensin cascade. A new study using a diabetic mouse model confirmed that combination treatment with paricalcitol (vitamin D analog) plus losartan (angiotensin receptor blocker) was effective in preventing the development of diabetic nephropathy (Dilip Deb et al, *Kidney International*, 2010).

SHOULD WE ANTICOAGULATE FOR ATRIAL FIBRILLATION IN DIALYSIS PATIENTS?

Atrial fibrillation (AF) is common in those with underlying cardiac disease, the elderly, and those subjected to recurrent hemodynamic stress: the hemodialysis population fits all three indices. Using the DOPPS data-base, Wizemann et al, *Kidney International*, 2010, demonstrated a 12.5% prevalence of AF in the hemodialysis population (higher prevalence in mid-European countries) with multiple treatment strategies reflecting national practice standards (coumadin in Canada, ASA in Japan, ACE inhibitors in Germany, digoxin in the United States, amiodarone in France, beta-blockers in Sweden, and calcium channel blockers by default). Solitary AF without underlying cardiac disease is typically a low-mortality illness, but dialysis patients generally have a 2-4x mortality attributed to AF. Though (embolic) stroke risk is 6x higher for non-dialysis patients with AF in comparison to those without AF, in the dialysis population the increased stroke risk attributed to AF is only 2x higher. Using the CHADS2 score system to triage benefit of long-term coumadin treatment (CHF, hypertension, age >75 yr, diabetes, stroke by history, TIA by history) the study suggests that CHADS2 identifies low risk patients but may misclassify others as high risk who do not really have a higher propensity for strokes. Coumadin did not always confer anti-stroke benefits in dialysis patients, being associated with higher CVS event rates, higher bleeding risks, propensity to vascular calcification, and overall higher mortality.

PARENTERAL TREATMENT OF HYPERTENSIVE CRISIS

The cardinal principle of treatment is rapid reduction in BP using a safe, effective, rapidly acting route which avoids intestinal malabsorption, emesis and delayed transmucosal transit, whilst at the same time titrating BP reduction carefully to avoid myocardial or cerebral ischemia (manifest as acute MI, visual loss or stroke). With the exception of adrenergic receptor blockers (alpha, beta, or combined), any of these drugs may provoke reflex tachycardia. The common drug options are:

1. Nitroglycerin 5-100 mcg/min: venous > arterial vasodilation, beneficial in ACS (acute coronary syndromes) or post-CABG though must have frequent BP monitoring to avoid precipitous (and unpredictable) drops in systolic BP.

PARENTERAL TREATMENT OF HYPERTENSIVE CRISIS *(Cont.)*

2. Nitroprusside 0.25-10 mcg/kg/min: combined arterial plus venous vasodilator, but too toxic (from thiocyanate/cyanide generation) for routine use.
3. Fenoldapam 0.1-1.5 mcg/kg/min: sustains preferential renal perfusion via dopamine-1 agonist effect, therefore beneficial in acute renal failure but do not use in glaucomatous patients.
4. Hydralazine 5-10 mg IV q 30-60 mins: arterial vasodilator which should never be used in ACS or aortic dissection, but is safe in pregnancy though may take up to 15-30 minutes for effect which lasts up to 2-4 hours, and may cause positive ANA serology even in the absence of lupus.
5. Labetolol 20 mg IV bolus q 20 mins or 2 mg/min infusion: combined alpha plus beta-adrenergic blocker, beneficial in ACS but may worsen cardiogenic shock, CHF, bradyarrhythmias or bronchospastic lung disease.
6. Nicardipine 5-15 mg/hr: safe and rapid onset, but hypotensive effect lingers longer, making titration difficult, therefore start very low and titrate upwards cautiously q 10 mins.
7. Clevidipine 1-16 mg/hr: also start low, titrate upwards cautiously q 5 mins, and has faster elimination kinetics meaning that this new calcium blocker will eventually replace nicardipine.
8. Phentolamine 5-15 mg IV boluses: starts to reduce BP within 1-2 minutes and lasts 5-10 minutes, being effective in catecholamine-related hypertensive surges from pheochromocytoma, tyramine reaction with cheese/MAO inhibitors, and cocaine toxicity.
9. Esmolol: used specifically to reduce shearing stress in aortic dissection, and less commonly in post-operative hypertension

HOW TO CHOOSE A STATIN

Not all statins (HMG Co A reductase inhibitors) are created equal. The choices are multiple, but the astute physician should base his decision on logic rather than who was the last visiting drug representative. All statins at lowest FDA approved doses can drop LDL cholesterol levels by 20-25% (almost double that amount for starting doses of Lipitor or Crestor), and 35-40% at the highest doses (which also increase drug adversity) except for Crestor/Lipitor which can drop levels by up to 50-60% at highest doses. The cardinal issues to consider in drug choice are:

1. Clinical potency: this is important where target LDL-cholesterol levels are unattained (usually for LDL goal <100 mg/dL), where end-organ damage (coronary artery disease) has already occurred, or where multiple CVS risk factors obtain; in those cases, use rosuvastatin (Crestor) or atorvastatin (Lipitor).
2. Potential drug interactions: Note that pravastatin (Pravachol) and rosuvastatin (Crestor) are not metabolized by the cytochrome oxidase system, and therefore are least likely to be affected by other drug interactions; fluvastatin (Lescol) is metabolized by cytochrome CYP2C9 which has few notable interactors, therefore making it relatively safe; artovastatin (Lipitor) is only minimally metabolized by cytochrome CYP3A4, which lessens its adversity profile; on the other hand, lovastatin (Mevacor) and simvastatin (Zocor) undergo extensive first-pass metabolism by CYP3A4 which system is strongly inhibited by azole antifungals, anti-retrovirals, clarithromycin, amiodarone, non-dihydropyridine calcium channel blockers and grapefruit juice.
3. Cost: which directly relates to the availability of generic alternatives, as is the case with Zocor, Mevacor and Pravachol.
4. Adversity: the major issues are myopathy (related to drug doses, concurrent use of cytochrome CYP3A4 inhibitors particularly for Mevacor and Zocor, and combination drug treatment with gemfibrozil), acute hepatic dysfunction, cognitive dysfunction including delirium, and clinical proteinuria (which appears to be common in CKD patients and those treated with Crestor).

DECODING DOWN'S SYNDROME

A recent *JAMA* Commentary by Einfeld & Brown, 2010, shows how far we have come in understanding trisomy 21. The critical region for Down's syndrome on the long arm of chromosome 21 encodes for two tyrosine-regulated protein kinase enzymes, which are overexpressed in vital brain (hippocampus, cerebellum, cerebral cortex) and cardiac tissues of the Down's patient. Those enzymes are believed to phosphorylate, and thereby "activate" the tau protein- a key step in forming amyloid plaques of Alzheimer's dementia, a universal finding in older Down's patients. More insidiously, those same protein kinases may encode a vascular endothelial growth suppressor, which might explain why Down's patients seldom develop solid cancers (but are prone to leukemogenesis). However, green tea contains a polyphenol, which can inhibit those same protein kinases, and reverse phenotypic changes of Down's syndrome in trisomic mice. Now comes news that Namenda, which is used for Alzheimer's disease, is equally effective in reversing learning deficits in Down's syndrome mice. Let the human trials begin!

ACUTE INTERSTITIAL NEPHRITIS

The key is early diagnosis, as immediate removal of precipitating cause (which in 80% of cases would be a therapeutic drug), is critical. Suspect AIN in any case of acute kidney failure (or sudden unexplained increase in serum creatinine) associated with either "sterile" pyuria (85%), fever (a third of cases), diffuse arthralgias (half of cases), eosinophilia (a third of cases), erythrocyturia (in two-thirds of cases) or evanescent skin rash. Identified causes include (a) medications (especially NSAIDs and beta-lactam antibiotics, as well as anticonvulsants, diuretics, allopurinol, proton-pump inhibitors and antiviral drugs); (b) systemic diseases such as SLE, sarcoidosis and Sjogren's syndrome (3S); © infections, including bacterial, viral and fungal disease; (d) about 5-15% are idiopathic. A "granulomatous" interstitial picture is uncommonly found on renal biopsy, which could be attributed to any of the above-mentioned causes, but are perhaps more indicative of systemic diseases including Wegener's granulomatosis, tuberculosis and BCG vaccination, paraproteinemia and multiple myeloma, IV heroin use, athero-embolic disease, and following jejunal-ileal bypass surgery.