Athens Kidney Center
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RETURN SERVICE REQUESTED

TREATMENT OF CANCER CACHEXIA

Cancer-associated cachexia represents a terminal hypercatabolic state in the cancer patient, denoted by reduced appetite, increased malaise, loss of lean body weight and adipose tissue. Treatment is uniformly unsatisfactory, in part because cachexia probably represents an inflammatory cytokine response to terminal disease. Efforts at nutritional supplementation and counseling are generally unhelpful. Current palliative treatment involves the use of:

1. Appetite stimulants such as Dexamethasone 2 mg p.o. BID or Megestrol acetate 400-800 mg p.o. q daily (best given as elixir) or medroxyprogesterone acetate 500 mg p.o. BID.
2. Anabolic steroids such as Fluoxymesterone 20 mg p.o. q daily or Oxandrolone 10 mg p.o. BID
3. Cytokine antagonists such as Thalidomide 200 mg p.o. q daily or omega-3 fatty acids 1200 mg p.o. q daily
4. Antidepressants such as mirtazapine 15-30 mg p.o. q daily
5. Cyproheptadine 8 mg p.o. TID has been used in carcinoid syndrome

However, none of these drugs have been shown to improve long-term outcomes or survival in cancer cachexia. Several other agents used for similar purposes- such as pentoxifylline, infliximab, etanercept, recombinant human growth hormone, ghrelin, Zofran, metoclopramide/Reglan are probably of little or no value in this syndrome. Whilst cannabinoids such as dronabinol are of proven effectiveness in HIV-associated cachexia, it is thought to be of no clinical value in cancer-related cachexia.

WALKING THE ART (ANTI-RETROVIRAL TREATMENT) GAUNTLET

Recommendations change with new knowledge and wider clinical experience. Current management guidelines recommend early, uninterrupted and aggressive combination drug treatment for life, preferably after testing for innate/acquired drug resistance, and closely monitored through HIV viral load (RNA level) and CD4 count. Presently, treatment-naive non-pregnant patients are typically started either on an NNRTI plus 2 NRTIs or alternatively, a PI plus 2 NRTIs. The most common combination is perhaps efavirenz/Sustiva (an NNRTI) plus tenofovir/Viread (an NRTI) plus emtricitabine/Emtriva (an NRTI). Efavirenz is very effective in combination with NRTIs but is associated with transient psychotic/encephalopathic side-effects; also, it cannot be used in pregnancy as it causes fetal (neural tube) defects. Tenofovir added to 2 other NRTIs in a triple-NRTI regimen often leads to virologic failure, and is therefore contraindicated. Emtriva is well-tolerated but tends to cause palmar-plantar hyperpigmentation (in Blacks, mostly). When efavirenz cannot be used, another NNRTI such as nevirapine/Viramune is often substituted. When Emtriva cannot be used, lamivudine/Epivir may be substituted.

Nucleoside/nucleotide HIV reverse transcriptase enzyme inhibitors (NRTIs) all tend to cause lactic acidosis, liver steatosis and peripheral lipoatrophy; class members include abacavir/Ziagen (which is associated with a high risk of acute MI, virologic failure in triple NRTI drug treatment, hypersensitivity mucositis in those with HLA B5701 allele), didanosine/Videx (which is associated with pancreatitis/gastroenteritis and peripheral neuropathy), zidovudine/Retrovir (which is associated with pancytopenias, hyperpigmentation of nail bed/oral cavity, and also antagonizes stavudine), tenofovir/Viread (which as noted above is associated with virologic failure in triple NRTI drug treatment, as well as progressive nephritis with proximal tubulopathy and Fanconi syndrome), lamivudine/Epivir (is typically well-tolerated), stavudine/Zerit (tends to antagonize zidovudine if used in combination), whilst emtricitabine/Emtriva is generally well-tolerated except for the cosmesis of palmar-plantar hyperpigmentation.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) generally have long plasma half-lives and must never be used as monotherapy if resistance is to be avoided; examples include efavirenz/Sustiva (which as earlier noted, causes a transient encephalopathy) and nevirapine/Viramune (which can be severely hepatotoxic).

Protease Inhibitors can induce both hepatotoxicity and peripheral lipoatrophy, examples including atazanavir/Reyataz (which causes a pseudo-Gilbert's syndrome, deposition of drug calculi in kidneys as well as prolongs the P-R interval), indinavir/Crixivan (which also causes drug-containing kidney stones), saquinavir/Invirase, and lopinavir (which is commonly sold in combination with another PI, ritonavir).

Entry-Fusion Inhibitors such as enfuvirtide/Fuzeon and maraviroc//Selzentry as well as Integrase Inhibitors such as raltegravir/Isentress (which could trigger rhabdomyolysis and renal failure in the vulnerable) are now relegated to clinical use as "second-line" agents.

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SECOND OPINION

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FROM THE EDITOR

I love the month of July: the renewal of heady summer days, the early rise of each morning sun, the steady creep in ambient temperatures, the lacework patina of evening dew and sweat, the promise of harvest and lingering nights..... but July is also a busy month. Kids are out of school, restless, all dressed-down, ready to go nowhere in particular; the mild intoxication of farmyard meals, hastily gathered, always late in the day..... the elixir of holidays enjoyed and imagined, a reappraisal of our place and mission down here on earth. I do love the month of July. This July, we will present new data on treating the very elderly- not an anonymous cohort of the dead and dying, but our aged brethren, who also are our mothers and fathers, and the grandparents of our children. We will discuss some of the clinical problems of current anti-retroviral therapy and x-ray new findings from the ever-expanding world of clinical cardiology and medical guidelines. I hope this edition captures both the ongoing drama of life and death- which is the bailiwick of medicine- as well as the languid pace of hot summer months, which ultimately, is the ambrosia that makes life itself worthwhile. Of course, such duality is nothing new to our professional calling: recall the symbolism of Aesculapius' caducceus, the mythologic depiction of cure and god-head, the superimposed leitmotif of Hebrew serpent on Aristotelian steadfastness. In that ancient iconography which juxtaposes predictability with anxiety (or primal fear), we embrace both Serpent and Staff, Pain and Bliss, Fall and Redemption, Birth and Death, Art and Science, Beginning and End. As it is in the journey of life, where the vigor of youth gives way to the infirmities of old age, it is in the July of our youth that we can contemplate the challenge of our December without blinking; it is said that only those who stand under the oak's leafy shade can stare directly at the sun's unforgiving glare. On such close inspection, we might rightly conclude that ICU care for our very elderly might not, after all, be such a good idea.

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

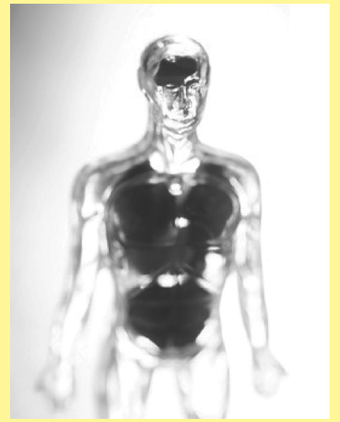
GOODBYE TO ALL NSAIDS?

In a particularly devastating month for NSAID use, Olsen et al, *Circulation*, 2011, report that even short-term NSAID use increased the risk of recurrent myocardial infarction (MI) and sudden death in patients with previous MIs. NSAID intake over only a 1 week duration increased the risk of death and recurrent MI by 45%, rising to 55% if NSAID use was over 3 months duration. As this finding appears to affect all NSAIDs except naproxen, and is maximal with non-selective NSAIDs (such as diclofenac), this study suggests that there is no therapeutic window of safety for NSAID use in the vulnerable cardiac population. Indeed, the cardiac risks for diclofenac were not only worse than noted for selective COX-1 antagonists (such as naproxen, and a lesser extent, ibuprofen), but even worse than were found for selective COX-2 antagonists (such as refecoxib/Vioxx, which was proscribed in 2004).

Another study carried out in mice and men, as published by Warner-Schmidt et al, *Proc Natl Acad Sci*, 2011, invoke the "cytokine hypothesis" of mental depression, which posits that depression is linked to higher neuronal levels of cytokines than are found in healthy controls. The study showed that NSAIDs decreased cytokine levels (mainly gamma-IF and alpha-TNF) in the frontal cortex, whilst serotoninergic anti-depressants (i.e. SSRIs) had the opposite effect. Indeed, NSAIDs reduced the clinical effectiveness of SSRIs in both New York mice and men: typically, 54% of depressed patients responded to first-line SSRIs, but with self-reported use of NSAIDs, that number dropped off to only 40%.

FASCINOMA OF MONTH: SEROTONIN SYNDROME

This syndrome of serotoninergic excess is characterized by altered mental status, neuromuscular excitability and autonomic instability. The syndrome is often provoked by excessive (and often concurrent) use of serotoninergic activators (such as anti-depressants, amphetamines [including the recreational pill, Ecstasy], narcotics/Ultram, Flexeril, anti-emetics, cocaine, Linezolid/Zyvox) or inadvertent combination of SSRIs with drugs that also block cytochrome P450 2D6/3A4 isoenzymes (e.g. erythromycin). Clinical diagnosis is based on a history of consistent drug use plus characteristic clinical findings (such as muscle/ocular clonus, agitation, tremulousness, diaphoresis, fever, diarrhea, and possibly, rhabdomyolysis and/or DIC). It is important to rigorously exclude differential considerations of drug withdrawal (based on history of alcohol/sedative abuse or narcotic dependence) and/or anti-cholinergic syndrome (which is often associated with TCA overdose and typically presents with agitation/delirium, raised vital signs with flushed skin, dry mouth and constipation) and/or neurolept malignant syndrome (based on a history of anti-psychotic drug use with hypersalivation, diaphoresis, raised vital signs, cognitive depression/coma, stiffness and reduced bowel sounds). Treatment of serotonin syndrome is supportive, with immediate discontinuance of offending drug(s), IV sedation for agitation/tremors, and PRN cyproheptadine for symptom control.



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TREATING HEART FAILURE WITH PRESERVED EJECTION FRACTION

Jong et al, *British Med J*, 2011, recently reviewed what is known and not known about heart failure with preserved ejection fraction a.k.a. diastolic dysfunction (i.e. ejection fraction >40%): it is as common as systolic dysfunction (i.e. patients with heart failure plus reduced ejection fraction), bears a high mortality at ~25% q year, carries a high morbidity (1/3 will be readmitted to hospital between 1-3 months), and shares similar demographics (though preservation of ejection fraction is statistically more common amongst women, chronic hypertensives, patients in chronic atrial fibrillation, and those without coronary artery disease). Unlike heart failure with reduced ejection fraction where ACE inhibitors (and to a lesser extent, ARBs), beta-blockers, aldosterone antagonists and implantable defibrillators have all been shown to reduce all-cause/cardiovascular mortality (though with little or no benefit on symptom control), no such benefits with respects to total mortality, hospital readmission or even symptom control has ever been shown in the case of heart failure with preserved ejection fraction. Impressively, all modalities of conventional therapy (ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists, digoxin, cardiac resynchronization therapy)- with the notable exception of defibrillator implantation- also reduced hospitalizations in those with reduced ejection fraction (systolic dysfunction), a feature that was also seen with candesartan (Yusuf et al, CHARM-Preserved Trial, *Lancet*, 2003), perindopril (Cleland et al, *European Heart J*, 2006) and digoxin (Ahmed et al, *Circulation*, 2006) in diastolic dysfunction. Jong et al recommend that treating diastolic dysfunction should be based on "first principles": diuretics for dyspnea, ACE inhibitor and/or beta-blocker if not expressly contraindicated, and digoxin for rate control in atrial fibrillation.

LEVAMISOLE AS DRUG SCREEN

Cocaine use is common and legal sanctions against recreational use are severe in the US; therefore, cocaine addicts often go to extreme lengths to hide ongoing drug use. Levamisole is an inexpensive, white powder commonly used as an anti-helminthic agent but also as an adulterant in "street cocaine". Chronic exposure to levamisole is known to cause leukoencephalopathy, cutaneous vasculitis (of the ear) and severe agranulocytosis. Buchanan et al, *JAMA*, 2011, demonstrate that the yield of cocaine metabolites in urine by gas chromatography/mass spectroscopy (which is less sensitive than drug detection by immunoassay) may be significantly improved by also checking for levamisole in samples. Moral: very few people have a legitimate reason for using levamisole in the United States, therefore positive urine levamisole screen = cocaine use.

SIX-POINT MANAGEMENT MODEL FOR ACUTE HEART FAILURE

Acute (or more accurately, acute-on-chronic) heart failure is a common and serious cause of hospital admission in the US: 1 million patients hospitalized q year, of which 30% will be readmitted and 15% will die within 3 months. Gheorghiade & Braunwald, *JAMA*, 2011, propose a 6-point management plan at initial presentation:

(1) Symptoms/Pulmonary Edema (confirm with chest film, start IV loop diuretic, consider IV vasodilation with nitroglycerin, mechanical ventilation if necessary, avoid IV inotropic agents especially in patients with CAD);

(2) Blood Pressure (elevated BP is often "reactive" from high sympathetic tone which often responds to IV diuretics, but elevated BP can also trigger heart failure from high cardiac afterload, and treatment is usually with systemic vasodilator; low BP often reflects low cardiac output, and portents poor outcomes especially in those with limiting [coronary] obstructive vascular lesions);

(3) Rhythm/Ventricular Response (both high and low pulse rate are deleterious: consider digoxin, short-acting beta-blocker for SVT);

(4) Triggers/Acute coronary syndrome (consider ACS; infections/pneumonia, pulmonary embolism, arrhyythmias, valvular rupture/incompetence, pericardial effusion/tamponade, poor therapeutic/dietary compliance, metabolic stress [pregnancy, AV fistula, malnutrition, thyrotoxicosis, anemia]; check cardiac enzymes/EKG: if acute coronary syndrome, include anti-platelet and revascularization modalities to routine cardiac care, otherwise reverse acute precipitant);

(5) Renal Failure/co-morbidities (especially CKD in cardio-renal syndromes, but also obesity, COPD/hypoxemia, diabetes mellitus);

(6) De novo/idiopathic (slowly progressive heart failure without identifiable trigger for acute clinical deterioration).

HOW TO TREAT UTI

1. Diagnosis of UTI is clinical: combination of dysuria plus frequency has a 96% positive predictive value in diagnosis.
2. Consider other diagnoses: vaginal discharge may indicate bacterial/fungal vaginitis or STD, flank pain/systemic features may suggest pyelonephritis.
3. Treatment should be empirical: waiting for cultures leads to unnecessary delays in treatment, and improvement in symptoms (within 48 hours) should be taken as proof of infection.
4. Drug of choice depends on clinical milieu: (a) Bactrim DS 1 tablet p.o. BID x 3 days (except in those with sulfa allergy or in south-central US where high resistance rates to drug are common) vs. (b) nitrofurantoin 100 mg p.o. BID x 5 days (ineffective against Proteus, Pseudomonas and Serratia spp; also avoid in patients with G6PD deficiency who are commonly of African or Mediterranean ancestry; the drug rarely causes neuropathy [in CKD], lung fibrosis [with chronic use], hypersensitivity hepatitis/pneumonitis) vs. (c) Ciprofloxacin 500 mg p.o. BID x 3 days (best reserved for initial treatment failures or infection with known "resistant" organisms or where pyelonephritis is suspected) vs. (d) Fosfomycin 3 g IV x 1 dose (where cost is no object, and compliance is uncertain).

TRAVEL MEDICINE: HOW TO REDUCE PHYSICAL RISK

Travel widens the mind as surely as it loosens the bowels. Though most death amongst travelers are due to drowning, automobile accidents and chronic illness preceding travel (mostly heart disease), most travelers are concerned about infections especially diarrhea and exotic infections, including malaria. Management of non-infectious complications are reviewed.

1. Motion Sickness: transdermal scopolamine applied behind ear 4-12 hours before onset of motion, change q 3 days; oral scopolamine 1 tab p.o. q 8 hours; promethazine 12.5-25 mg p.o. q 4-6 hours PRN.
2. Venous Thrombosis: drink extra non-alcoholic fluids, avoid diuretics and stimulants/caffeine, walk along aisle q 2 hours, dorsiflex/hyperextend feet q 30 mins, wear thigh-high compression stockings during flight, consider Lovenox 40 mg sq x 1 in high risk patients (previous DVT/PE, morbid obesity, thrombophilia, underlying malignancy, nephrotic syndrome).
3. Jet Lag: shift sleep-wake cycle to prevailing time at destination point; drink extra fluids; take short naps; melatonin 1-5 mg p.o. q HS x 1-5 days; zolpidem 5-10 mg p.o. qHS x 3 days.
4. Altitude Illness: gradual ascent to 8000 ft elevation; extended (2+ day stay) at half-way point for acclimatization; acetazolamide 125-250 mg p.o. BID starting 2 days before ascent and continuing for 2 days after ascent; oxygen supplementation at night (as needed); dexamethasone 4 mg p.o. QID (for cerebral edema).

SHOULD WE STOP SCREENING FOR PROSTATIC CANCER?

Prostate cancer is rightly feared as a common and deadly illness. Cure relies on early diagnosis and surgical extirpation. However, not all prostate cancer is lethal: more people die with their prostate cancers than die from them. Furthermore, there are few reliable techniques for selecting out aggressive disease from slow indolent neoplasia. Screening has traditionally relied on serum PSA levels and/or digital rectal examination. Djulbegovic et al, *British Med J*, 2010, perform a meta-analysis of 6 relevant randomized screening trials, and conclude that screening for prostate cancer did not improve cancer-specific or all-cause mortality in the "average" male population. So, next time your urologist asks you to bend down....

PREDICTING STENT THROMBOSIS AFTER PTCA

HORIZONS-AMI trialists report in Dangas et al, *Circulation*, 2011, that in-situ stent thrombosis occurred within 2 years in 4.4% of recipients following PTCA for ST-segment elevation myocardial infarction. Thrombosis was not predicted by type of stent (bare metal or drug-eluting) and appeared similar in those randomized to either bivaluridin monotherapy vs. unfractionated heparin plus glycoprotein IIb/IIIa inhibitor, those patients on bivaluridin monotherapy tended to thrombose preferentially within the first 24 hours of PTCA, suggesting an adjunctive role for aggressive anti-platelet therapy in that sub-group.

THE SIGNIFICANCE OF LOW TSH

Low serum TSH levels signify either physiologic suppression of TSH secretion by overt or subclinical thyrotoxicosis (endogenous overproduction of thyroid hormone, exogenous administration of thyroid hormones as replacement therapy for hypothyroidism or suppressive therapy for thyroid cancer) or low pituitary TSH synthesis from so-called "euthyroid sick syndrome", neuropsychiatric disorders (including affective disorders as well as hypothalamic-pituitary diseases) and high-dose dopamine/steroid therapy. The true clinical importance of a low TSH profile is the detection of subclinical hyperthyroidism (in the elderly).

POSSIBLE INDICATORS OF HIV CARDIOMYOPATHY

A recent observational study amongst 8486 veterans followed over 7+ years by Butt et al, *Arch Intern Med*, 2011, show that HIV-positive veterans had an 81% higher risk of cardiac failure, which was not explained by underlying coronary artery disease, chronic arterial hypertension, cardiac valve disease or alcohol use. Cardiac failure was particularly associated with high viral loads >500 copies/mL, which seems to indicate that ongoing viral replication is causally related to cardiac failure in this cohort. It is unclear if early and aggressive anti-retroviral treatment would necessarily reverse this syndrome.

WHICH VITAMIN D IS THE FAIREST OF THEM ALL?

Vitamin D is the new "wonder pill", therefore, formulating the optimal vitamin supplement has become a holy grail. As true vitamin D deficiency is uncommon, it has become clear that vitamin D use is powered by the more recent clinical description of vitamin D insufficiency, which occupies the biochemical middle ground between frank vitamin D deficiency (characterized by rickets or osteomalacia with serum 25-hydroxy-vitamin D levels under 10 ng/mL) and normal vitamin D status (where serum 25-hydroxy-vitamin D levels are equal or over 20 ng/mL). Therefore, vitamin D insufficiency is denoted by serum 25-hydroxy-vitamin D levels between 10-20 ng/mL and is (almost inexplicably) associated with frequent falls, fractures, mental illness/schizophrenia, depression, allergic diathesis, renal failure (in Blacks), type 2 diabetes mellitus and insulin resistance syndromes, infections (largely attributed to macrophage inaction, possibly as a result of reduced cathelicidin expression) as well as excess cardiovascular morbidity and all-cause mortality. Vitamin D status itself depends on both ill-defined as well as known variables which include age, activity, sunlight exposure, race/skin pigmentation, dietary vitamin D intake and obesity. Heaney et al, *J Clin Endocrinol Metab*, 2011, report on the effects of dosing patients with equimolar amounts of either vitamin D2 (ergocalciferol) or D3 (cholecalciferol) at 50,000 units/week over a 3 month period. Vitamin D3 (cholecalciferol) was found to be 87% more potent in raising serum levels of 25-hydroxy-vitamin D and 200-300% better at improving vitamin stores.

DO THE VERY ELDERLY GAIN FROM ICU CARE?

Appropriate treatment of the very elderly population is an emotive issue, fraught with scientific, ethical, political and legal risk: remember that the elderly vote (almost unfailingly). Recall that despite conventional dogma to the contrary, supported by the INDANA Group meta-analysis (Gueyffier et al, *Lancet*, 1999) indicating that only stroke incidence was reliably reduced by anti-hypertensive treatment amongst the very elderly, achieved at a considerably high risk of increased all-cause mortality, Beckett et al, *N England J Med*, 2008, clearly showed the overall beneficience of adequate anti-hypertensive treatment in the very elderly. Now comes Boumendil et al, *Arch Intern Med*, 2011, on behalf of the ICE-CUB Study Group who carefully analyzed the impact of ICU admission on mid-term and long-term outcomes in the very elderly over a 14 month period in a prospective observational cohort study. Verdict: no benefit was found from ICU admission in this sub-group.

DO NOT ORDER LIST

The National Physician Alliance has come out with a laundry list of investigations that ought not be ordered, based on a proven lack of health benefit to the patient, as well as an added risk of patient harm and unnecessary financial cost:

1. No BMP/CMP or UA in screening asymptomatic healthy adults.
2. No cardiac screening tests/EKG for screening asymptomatic low Framingham-score, low risk adults.
3. No DEXA scans for screening osteoporosis in anyone under 65 y.o. or men without risk factors who are under 70 y.o.
4. No imaging tests for low back pain without "red flags for malignant causation" in the first 6 weeks of management
5. No antibiotics for acute mild/moderate sinusitis within first 7 days
6. No Pap test on women younger than 21 y.o. or those S/P hysterectomy
7. Prescribe only generic statins.

Any questions?

THERAPEUTIC COMPLIANCE AS DRUG CLASS EFFECT

As NHANES routinely reminds us, chronic arterial hypertension is common, often untreated, and commonly uncontrolled. A recent meta-analysis by Kronish et al, Circulation, 2011, suggests that compliance with anti-hypertensive drug therapy depends on drug class: patients on (costly) ACE inhibitors and ARBs tend to be most adherent, patients on diuretics and beta-blockers are least compliant. This study proves that it is not primarily cost or availability that drives long-term drug compliance, but tolerance (to side effects).