Athens Kidney Center
1440 North Chase Street
Athens, GA 30601

RETURN SERVICE REQUESTED

COCAINE TOXICITY

Cocaine ingestion blocks norepinephrine re-uptake at nerve terminals simulating an adrenergic surge, plus secondary effects such as sodium channel antagonism (thereby blocking the generation and transmission of neurogenic action potentials), serotonin/dopamine reuptake inhibition (which augments adrenergic overactivity), and CNS dopaminergic stimulation (especially in the ventro-basal nuclei, believed to be the basis of its euphoric effects). The clinical effects of cocaine intake are multi-systemic, best captured with the mnemonic, "HADES RAT" (rat from hell): hyperthermia/hypertension, agitation, delirium, eyes dilated, seizures, rhabdomyolysis/respiratory impairment (including non-cardiogenic pulmonary edema/ARDS), arrhythmias, tremors/twitches. This adrenergic toxidrome may mimic anticholinergic drug overdose (which is differentiated by urinary retention, reduced bowel sounds and normal BP levels), thyrotoxicosis, neurolept malignant syndrome, serotonin syndrome and metabolic encephalopathy. There are no antidotes for cocaine toxicity. Treatment lies in prompt stabilization (assure airways, vital signs and cardiac monitoring); sedation with benzodiazepine; complete toxicology screen; consider lidocaine/amiodarone for ventricular arrhythmias (beware torsades de pointes); use of beta-blockers is controversial (recent studies suggest that beta-blocker use may be acceptable); rule out CNS bleeding; consider co-toxicity with added impurities (notably amphetamines, heroin, talc powder, quinine, strychnine, lidocaine and other hallucinogens). Peak effect of cocaine use occurs within 90 minutes regardless of route (within 15 mins if taken IV); progressive toxicity after arrival to ED should suggest "body packing".

CLINICAL APPROACH TO GOUT

Gout is the price primates (as well as Dalmatians) pay for lacking the enzyme, uricase, which converts uric acid to water-soluble allantoin. Gout has a bimodal therapeutic plan: acute gout, which focuses on pain relief and resolution of acute crystal synovitis; chronic gout, on the other hand, focuses on prophylaxis by reducing serum uric acid levels. Acute gout: colchicine 0.6 mg p.o. at onset of symptoms, repeat q hour x 2 extra doses, then 0.6 mg p.o. q daily x 1 week to prevent "rebound"; prednisone 40-60 mg p.o. q daily x 3 days, then taper over 1 week; depot ACTH 20-80 IU given IM, repeat after 48 hours; low-dose NSAID (ibuprofen 400-800 mg p.o. TID x 5 days or indomethacin 25-50 mg p.o. TID x 5 days); anakira 100 mg SQ daily x 3 days (this potent IL-1 antagonist has not been approved by FDA); canakinumab 150 mg SQ single dose (this potent IL-1beta antagonist has not yet been approved by FDA).
Chronic gout: dietary manipulation (low purine diet with restricted red meat, beer and shellfish, as well as avoidance of high fructose sweeteners, alcohol and vitamin C); allopurinol 100-800 mg p.o. QD (titrate dose to obtain serum uric acid <6 mg/dL, but this xanthine oxidase inhibitor cannot be given during or soon after acute attack, and should not be given with azathioprine); febuxostat 40-120 mg p.o. QD (cannot be given with azathioprine, theophylline or 6-mercaptopurine); pegloticase 2-8 mg IV infusion q 2 weeks (not to be given as IV bolus and cannot be used in G6PD deficiency); probenecid 500 mg p.o. BID (this uricosuric agent must be given with sodium citrate to alkalinize the urine).

SWITCHING FROM PERITONEAL DIALYSIS TO HEMODIALYSIS

Though both modalities for renal replacement treatment, peritoneal and hemodialysis, are assumed to be roughly equivalent, new data from Szeto CC et al, Nephron Clin Practice, 2010, shows that those who started with peritoneal dialysis and later switched to hemodialysis have an excess mortality compared to their demographically-matched peers who started and remained on hemodialysis. The excess mortality over 5 years was about 20%, though most of the mortality occurred within the first year following PD-HD switch. Independent predictors of mortality in peritoneal dialysis patients who switched to hemodialysis include duration of peritoneal dialysis as primary renal replacement regimen; medical co-morbidities; residual renal function (persisting despite renal replacement treatment), and fat-free, edema-free body mass index. A possible reason for this disturbing finding is that the most common trigger for switching treatment modalities in most dialysis patients is failure to thrive.

HELPING ERYTHROPOIESIS IN KIDNEY FAILURE

The causes of anemia in renal failure are multi-factorial: hemolysis, nutritional deficiencies, "vampire syndrome" from multiple blood draws, reduced erythropoetin levels, end-organ resistance to erythropoietin, oxidative stress, et cetera. A new study from Taiwan suggests that Mucomyst 200 mg p.o. TID for 3 months in dialysis patients was associated with improved anemia indices, a 30% reduction in Procrit dosage, and reduced LDL cholesterol levels, presumably due to reduced oxidative stress (Hsu S-P et al, Nephron Clin Practice, 2010). Now, just try getting your dialysis patients to take oral Mucomyst TID!

AUTOIMMUNE ENCEPHALOPATHY

Acute/subacute cognitive impairment of unknown cause is a common and distressing clinical condition. Sometimes diagnosed as "acute dementia" or "limbic encephalitis" in the ICU setting, the key is a systematic approach in management: exclude encephalo-meningitis by appropriate blood/CSF tests and cultures; exclude seizures (complex partial epilepsy is the most notorious confounder) by EEG evaluation and clinical course; review all medications for possible drug-induced reaction and complete a blood/urine drug screen (search for psychotropic and anti-cholinergic drugs); search for CSF evidence of pleocytosis and/or elevated protein count; rule out endocrinopathy (e.g. Hashimoto's encephalopathy with anti-peroxidase antibody profile), vasculitis (including lupus and microscopic polyarteritis), pernicious anemia (vitamin B12 levels) and low-grade infections (including HSV, HIV, Creutzfeldt-Jakob and treponemal diseases). Where appropriate, test for neuronal auto-antibodies. In a recent study by Flanagan EP et al, Mayo Clin Proc, 2010, two-thirds of these patients responded to immunotherapy which included steroids, plasmapheresis and IV immunoglobulin treatment.

the
SECOND OPINION

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FROM THE EDITOR

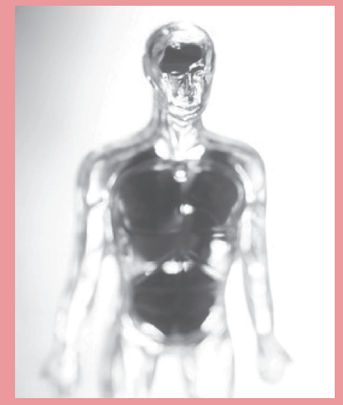
The marriage of medicine to politics is rarely a pretty sight: the courtship is clumsy, spousal abuse- or at least, indifference- is standard, the progeny are handicapped, and there is enough guilt to stifle any chance of lasting pleasure. Which might explain why we don't have a lot of physician-statesmen. There are, of course, exceptions to the rule: John Locke was an influential political theorist, but disdained the hand-to-hand combat of Westminster; Augustinho Neto, late of Angola, was a visionary in the Marxist mold, as was the tempestuous Che Guevera, who was destined to die young. Chile's Michelle Bachelet is past muster, but probably not Syria's Bashir Al Assad, who is infinitely better at removing cataracts than living at peace with his neighbors. Britain's Lord David Owen was a formidable diplomat, save for his somewhat disconcerting trick of diagnosing visiting potentates with obscure medical disorders; he achieved lasting notoriety for diagnosing Russia's president Chernenko's emphysema through a handshake. As would be expcted, the Queen was not amused.

The reasons are probably rooted in the dissonant traditions of medicine and politics; doctors, by their training, are individualistic and questioning; politics is the art of consensus and compromise. Medicine strives for quality, and sometimes, the grail of perfection and certitude. Politics is dependent on cycles, emotion and shifting interests: a vote in hand is worth twenty oaths of undying fealty.

Nearer home, the track record of physicians in politics is even spottier, and arguably, ex-Senator Bill Frist is primus inter pares. But that might soon change: the lackluster attempt by the Obama administration at health-care overhaul has left the "loyal" left unfulfilled and the "righteous" right frothing at the mouth, in turn triggering a tidal wave of physician-aspirants to congressional power. Mid-term elections are, after all, the first official sign of fall, as well as the advent of the silly season. 'Tis the season to celebrate the pagan pastime of Halloween, when consenting adults and their children make-believe they are ghouls; the time-honored repast of Thanksgiving, providing an opportunity for dysfunctional families to gather around tables of Discontent for the annual ritual of false nostalgia and mutual antipathy; and, of course, Christmas, when material excess is celebrated in the name of a poor, itinerant carpenter from Galilee. Which brings us back to a New Year, which fosters our resolve to change the effete and banal, but keep in place the roots of our collective discontent.

The opening salvos of this mid-term election have been great theater: a drowning gubernatorial gladiator out of Rhode Island (my old hunting grounds, I should add) has asked the President to "shove it", meaning his presidential endorsement, in a fit of rhetoric excess. His unlikely parody of Congressman Joe Wilson of South Carolina proves that imitation remains the sincerest form of flattery. In Delaware, the senatorial race pits a rather bland Democratic candidate against a femme fatale from hogwash- pardon me, hogwarts. Not to be outdone, Hollywood presents a modern parable straight from Rambo III: ex-governor Jerry Brown, well tanned, faintly lisping, hooded brows and accoutered in black (there must be some subliminal message there) against Meg Whitman of the eBay billions. The loser will be consigned to Valhalla-give or take a couple hundred millions of dollars- which, come to think of it, is not necessarily a bad idea. Our republic is outraged at the size of a metastasizing government: hell no, we do not want government in our lives- except for Medicare, Medicaid, Social Security, Pell grants, small business loans, unemployment benefits, the whole works. And such is the irony of life- and politics.
I'll see you Friday lunch-time, at the CME lounge.

Beze Adogu, MD, Ph.D, FACP



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NON-RESPONSIVENESS TO HEPATITIS B VACCINE

An estimated 5-10% of recipients do not respond to hepatitis B immunization, as defined by failure to develop anti-hepatitis B surface antibodies. Those recipients remain susceptible to hepatitis B infection. For those at high risk of exposure to hepatitis B such as in-center hemodialysis patients, health-care workers and IV drug users, it is important to develop new strategies to overcome resistance to routine immunization. Factors responsible for non-responsiveness to HBV vaccination include genetic and acquired factors, such as obesity, older age, smoking history and high baseline ALT levels. Strategies to overcome non-responsiveness include:
Repeat immunization protocol (0 month, 1 month, 6 month) using double the normal dose of antigen.
Administer hepatitis antigen intra-dermally (instead of intramuscularly) (Levitz et al, IC & H Epidemiology, 1995).
Repeat immunization protocol with regular-dose HBV antigen intramuscularly combined with granulocyte-macrophage colony stimulating factor (GM-CSF)(Nyong-Jin et al, Vaccine, 2003).
Double-dose combination of hepatitis A and hepatitis B antigen (2 ml of combined vaccine) to trigger specific heterologous immunity in >80% of non-responders (Cardell et al, J Infect Dis, 2008).
Only option #4 appears to show clinical promise.

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ADVANCED MATERNAL AGE

There has been a change in the counseling of the "older" pregnant patient, defined by age > 35 years. Previously, age was the primary determinant of risk, and was used to decide whom to counsel concerning increased risk of trisomy 21 (i.e. Down's syndrome), based on a "cut off" at 35 years of age. The rationale for this practice was because at age 35, the risk of invasive testing (i.e. amniocentesis, chorionic villus sampling) was about the same as the risk of finding a fetus with Down's syndrome. Consequently, testing was not usually offered to younger age patients and older patients were routinely referred for amniocentesis or chorionic villus sampling. It was soon obvious that this simple algorithm was defective: we were missing the majority of cases with Down's syndrome (because so many more pregnancies occur in the younger age group, and whilst individual risk was lower in the younger patient demographic, population risk was significantly higher than is present in the much fewer "older" pregnancies) and we were losing a significant amount of normal pregnancies (due to procedure-related complications of testing). Maternal serum screening was introduced to help resolve this dilemma: however, its relatively high false positive rate (10-15%) and low detection rate (70%) meant that patients with advanced maternal age (above 35 years of age) were still considered a particularly high-risk group, and were accordingly, treated differently. The advent of first trimester screening using a combination of fetal ultrasound plus maternal blood screening, has improved our ability to detect Down's syndrome (90%) with a low false positive rate (5%) in all tested mothers. The somewhat pejorative label "advanced maternal age" has essentially been deleted from routine medical use. Now, all patients, regardless of age, are offered first trimester screening for possible trisomy 21 in the fetus, and the results are then used to determine who is really "at risk" regardless of maternal age. In this scenario, patients in their early 40s may return with "normal" or "average" risk and avoid further invasive testing, and teenagers may present with "increased" risk, thus triggering invasive testing such as amniocentesis. Regardless of the results, we generally offer a detailed ultrasound at 18 weeks gestation looking for structural abnormalities that might be suggestive of Down's syndrome or any other chromosomal abnormality. If a mother's first trimester screen and 18 week ultrasound report are deemed "normal", the risk for fetal trisomy becomes so low (regardless of maternal age) that further testing is generally not indicated. *CONTRIBUTED BY RICK ROSEMOND, MD (MATERNO-FETAL MEDICINE)*

IS CORONARY ARTERY DISEASE GENETIC?

Atherosclerotic disease in the coronary circulation and elsewhere shows a familial clustering. Yet, it has long been regarded as an acquired condition; after all, families share more than common genes and ancestry. Families, unfortunately, also tend to share bad habits and deleterious lifestyles. Recent genome-wide association studies have identified genetic variants of the chromosome 9p21 locus as important determinants of future CAD (Samani NJ et al, N England J Medicine, 2007). The locus is adjacent to cyclin-dependent kinases (such as CDKN2A) which govern cell proliferation, apoptosis and cell death, and also encodes an RNA gene called ANRIL (anti-sense non-coding RNA of INK4 locus) which is thought to be important in cellular atherogenesis and is highly expressed in the myocardium. These same variants may predict poor outcomes with a high risk of fatality within 5 years following coronary artery surgery (Muehlschlegel JD et al, Circulation, 2010).

ACUTELY EXACERBATED COPD PHENOTYPE

There appears to be a small but distinct sub-group of frequently exacerbated COPD patients (editorial: Tashkin DP, New England J Medicine, 2010). The ECLIPSE study shows that such exacerbations occur 4.4-7.3x more frequently in this group than is seen in "typical" COPD patients (Hurst JR et al, New England J Medicine, 2010). Exacerbations occur often regardless of the severity of underlying COPD; in other words, frequency of acute exacerbations do not reflect the severity of chronic lung disease itself. Frequent exacerbators generally have a poor quality of life, and are stigmatized by high WBC counts. The reason(s) for frequent exacerbations are unknown, but candidate etiologies include: poor therapeutic compliance; micro-aspiration of gastric contents from undiagnosed GERD; increased susceptibility to lung infections; under-treatment of underlying disease, and of course, continued exposure to lung toxins (such as cigarette smoke).

SEVERE HYPOGLYCEMIA IS VERY BAD FOR YOU

The ADVANCE trial- a gift which keeps on giving- continues to highlight the dangers of severe hypoglycemia in type 2 diabetes mellitus. Not only does intensive glycemic control apparently show little or no benefit in type 2 diabetics, the long-term effects of severe hypoglycemia are protean: 3.5x risk of major macrovascular event, 2.2x risk of major microvascular event, 3.8x risk of cardiovascular disease, 2x risk of cancer, 2.2x risk of digestive tract disease/event, 2.5x risk of lung disease/event an d 4.7x risk of skin disease Zoungas S et al, New England J Medicine, 2010). What is unclear is whether hypoglycemia itself predisposes to these conditions (unlikely) or identifies a metabolically vulnerable group that is susceptible to multiple complications (likely).

THE BINGEING HEART

Finally, we can learn from young, adroit German drinkers what happens to the heart after a vodka binge (Zagrosek A et al, JAMA, 2010). At an average peak blood alcohol level of 0.13 g/dL, cardiac MRI revealed myocardial inflammation and edema with preserved LV function; 50% had serologic evidence for myocardial injury as shown by elevated troponin I levels, and 12% developed a small pericardial effusion (as probable evidence for pericarditis). All the changes were reversible after 1 week. Now, consider the probable outcomes if those were older volunteers or recurrent binge drinkers or those with underlying heart disease.....

HANDS-ONLY CPR BY BYSTANDERS

Cardiac arrest is common, treatable and fatal. The key is to begin resuscitation immediately and properly. For that to happen, the public must become better educated, less squeamish, and more goal-directed. Time is heart. The great state of Arizona, happily in the news for something besides immigration reform, is leading the way by encouraging state-wide bystander "hands-only" CPR. The results are excellent. Bystander CPR rates for out-of-hospital cardiac arrests improved from 28% to 40%, with almost tripled survival figures. Indeed, "hands-only" CPR appeared to work better than "no CPR" (no surprise there) as well as "full hand-mouth" CPR, independent of age, gender, cardiac rhythm, EMT response time, location of cardiac event or EMT post-CPR protocol (Bobrow BJ et al, JAMA, 2010). Sadly, brain recovery remains poor at under 5%.

TREATMENT OF HYPONATREMIA

1. First confirm diagnosis by demonstrating low serum osmolality.
2. Assess risk of ongoing or impending cerebral edema: look for visual, respiratory or focal/diffuse neurologic changes, and based on risk profile (cerebral edema is more common in young, females, hypoxemic/lung disease, underlying brain injury and Ecstacy use), acuity of onset (brain adaptation is incomplete under 48 hours) and severity of hypo-osmolality (under 115 mmol/L is severe) plan for IV hypertonic saline at 1mL/kg/hr (this dose may be doubled or tripled for patients with active seizures or signs of brain stem herniation until serum sodium is elevated by 6 mmol/L).
3. Assess volume status: hypervolemic (cardiac failure, cirrhosis, nephrotic syndrome, COPD) vs. euvolemic (thiazide abuse, low-reset osmostat in pregnancy, post-operative, hypothyroidism, hypopituitarism, adrenal failure, essential hyponatremia of elderly, SIADH) vs. hypovolemic (gastroenteritis, severe burns, "third-spacing", hypoalbuminemia, salt-losing nephritis, inappropriate diuresis).
4. Titrate treatment based on volume status: hypovolemic (stop all diuretics, consider steroid treatment if addisonian, start IV normal saline, avoid aquaretics); hypervolemic (fluid restriction <0.8 L/day, salt restriction, loop diuretics only, treat underlying cause); euvolemic (fluid restriction <1.2L/day, salt supplementation, loop diuretics, increase solute intake, correct underlying cause, stop all medications linked to SIADH, consider aquaretics).
5. Correct serum sodium slowly: aim for a gradual increase of no more than 12 mmol/L each day; if over-correction occurs, stop IV hypertonic saline, and reverse spike in serum sodium level with IV dextrose 10% or desmopressin.
6. Chronic treatment: demeclocycline 300-600 mg p.o.BID (takes 2 weeks to act, cannot be used in liver disease); lithium (300 mg p.o. TID) causes nephrogenic diabetes insipidus; phenytoin 100 mg p.o. TID (only in post-traumatic hyponatremia); urea 30-90 g p.o. q daily (used only in Europe); aquaretics (vasopressin V2 receptor antagonists which is given IV as conivaptan [20 mg IV bolus over 30 mins then 20-40 mg IV continuous infusion daily for maximum of 4 days] or orally as tolvaptan [15-60 mg p.o. QD]).
7. SIADH is a diagnosis of exclusion and is typically associated with degenerative/inflammatory or neoplastic/vascular lesions of the lungs or central nervous system (including acute porphyrias, thymomas, acute asthma, pneumothorax, IPPV, acute brain bleeds and psychotic episodes); several drugs have been implicated in SIADH including anti-psychotics/anti-depressants, hypoglycemic drugs and narcotics.

A NEW DRUG FOR LYMPHOMAS

Hallek M et al, Lancet, 2010 report a substantial increase in progression-free survival in treatment-naive, treatment-refractory and post-treatment relapsing cases of chronic lymphocytic lymphoma (CLL) with chemoimmunotherapy. This was achieved by adding rituximab (a chimeric mouse monoclonal anti-human CD20 antibody) to standard fludarabine plus cyclophosphamide combination. Survival was at the cost of higher neutropenia risk, though without a corresponding increase in "secondary" infections. The scope of rituximab in oncology is steadily expanding, now including follicular lymphomas (expanding the standard CHOP or CVP regimen of cyclophosphamide, doxorubicin, vincristine and prednisone) and other indolent leukemias. Unfortunately, not everyone responds to rituximab: those with a 17p deletion are immune to the beneficience of this drug in CLL.

CIRCUMCISION AS HEALTH STRATEGY

Several reports have shown that male circumcision reduces the risk of HIV infection amongst heterosexual males by 60%. A new study (Gray RH et al, PLoS, 2009) funded by the Fogarty and Gates Foundations in Rakai, Uganda, suggests that the reason for this relative protection primarily lies in the removal of HIV target cells ordinarily resident in the foreskin, and only secondarily (about 10% reduction) attributable to a lower incidence of genital ulcers (from herpesviruses, trauma and other STDs).

POLYPHARMACY

Polypharmacy is common, lethal and discriminatory: the oldest and sickest of us are at highest risk. This occurs in all health-care settings, is (mal)practiced by all physicians at some time, leads to multiple symptoms which are often wrongly ascribed to aging or a new disease process. The results are higher treatment costs, reduced quality of life, more drug-disease and drug-drug interactions, more complications (falls, anorexia, impaired biological functions, delirium, altered cognitive process, et cetera) and high prevalence of subclinical drug toxicities. Polypharmacy includes using multiple drugs (usually defined as >5 by any patient), taking more drugs than is clinically necessary (even if relatively few in number), or having a high pill burden (even if all pills are clinically indicated). Data shows that 70% of all office visits terminate with a prescription, that 30% of those prescriptions are unnecessary, and the elderly receive 3 or more individual prescriptions at 30% of office visits. Doctors do not like being perceived as uncaring ("She's in so much pain, Doc") and are not typically trained in geriatric pharmacology; patients often shop from different doctors and different pharmacies, in addition to hoarding a virtual cocktail of OTC drugs (which are never volunteered on casual inquiry) and "herbal supplements" (from kind Aunt Missy down the road). The result is that medications are now the #5 cause of death in America. As Gurwitz reminds us: "any new symptom in the elderly should be considered a drug-induced reaction until proven otherwise". The elderly are at highest risk because of altered drug handling and drug effects in the aging body (pharmacokinetics, pharmacodynamics) as well as the higher prevalence of co-morbidities, which do not always need to be treated in the first place. Even worse, a large percentage of those co-morbidities were triggered by medications in the first place (and treated in turn by more medications in an ever-widening "prescription cascade"). A common example in nephrology: diagnosis of hypertension- treat with calcium channel blocker- patient develops ankle edema- treat with diuretic - patient develops hypokalemia - treat with KCl pill- patient develops gastric ulcer - treat with Zantac- patient reports with delirium- add Valium. What can we do? First, some reassurance: drugs can be safely discontinued in the elderly within the community setting without much risk in over 80% of cases (Garfinkel D & Mangin D, Archives Intern Med, 2010).

1. Every patient must be educated that any non-food additive is a drug (otherwise, we'd call it candy).

2. Every doctor must try to use the right drug at the right dose for the shortest possible duration.

3. Document all drugs taken (prescription or otherwise); encourage patients to seek only 1 pharmacy; notify the primary MD of all prescription changes.

4. Highlight high risk drugs based on their high risk/benefit ratio, narrow therapeutic index, renal/liver elimination profiles, et cetera: beta-blockers, anti-depressants, psychotropics and stimulants, pain medications, supplements/vitamins.

5. Closely monitor all drugs with narrow therapeutic index (digoxin, cyclosporine, coumadin, phenytoin, lithium, theophylline).

6. Optimize all prescriptions: avoid duplications (e.g. 2 different types of ACE inhibitors), remove redundant pills (e.g. PPI and histamine-2 blocker), adjust drugs for renal function, adjust drugs for liver metabolism, flag drugs with anti-cholinergic effects, cancel any pill not used in last 2 weeks, generate a "do not use" list for the elderly (e.g. no meperidine [use Ultram], no long-acting benzodiazepines, no chlorpromazine, no amitriptyline/imipramine [use nortriptyline/desipramine]).

7. Beware physician inertia: do something!

INTRA-DIALYTIC HYPERTENSION

Surges in blood pressure are common during hemodialysis treatments, and could lead to cardio-vascular crises. Intradialytic hypertension is defined as >12 mmHg rise in mean arterial pressure during dialysis treatment, and is said to occur in about 12% of all treatments. Commonly, intradialytic hypertensives are associated with a higher hospitalization rate, more prevalent cardiac failure, and increased overall mortality. There are several putative causes for intra-dialytic hypertension. The commonly cited underlying triggers include: volume overload; increased cardiac output (which may itself be attributed to high AV fistula flows); renin angiotensin aldosterone system (RAAS) activation by intra-dialytic hypovolemia; sympathetic overactivity during treatment (which may be physiological to stress/hypovolemia, pathological, or pharmacological from illicit drug use); endothelin-induced systemic vasoconstriction; sudden shifts in plasma calcium/potassium levels; systemic clearance of anti-hypertensive drugs during treatment (most notorious in this regard are beta-blockers and ACE inhibitors and vasodilators); systemic vasoconstriction secondary to hyperviscosity (e.g. from hemoconcentration or IV albumin treatment) or following high-dose IV Procrit treatment. Treatment is focused on slow, cautious ultrafiltration targeting a 8-12% reduction in body weight over weeks/months. Other aspects of treatment include dietary salt restriction, avoidance of "sodium modeling" during treatment, extended treatment times (to enable slow ultrafiltration), substitution of dialyzable anti-hypertensives (the ACE-inhibitor fosinopril does not dialyze out, and hydralazine is safe amongst the vasodilators, whilst carvedilol/bispropol are acceptable beta-blockers) and fluid restriction at home.

SYSTEMIC CAPILLARY LEAK SYNDROME

This rare disease is likely under-diagnosed; we have seen several suspected but not confirmed cases over the years. The syndrome is thought secondary to transitory (and probably cyclical) endothelial dysfunction leading to a reversible plasma extravasation into the subcutaneous tissue ("third spacing"). Ingredients of clinical diagnosis are a brief prodroma leading to a shock-like state with hypotension, vascular instability/collapse, hypoalbuminemia, hemoconcentration (including thrombocytosis and/or leucocytosis, therefore leading to an initial impression of sepsis syndrome) and monoclonal gammopathy (in 80% of cases). Complications could include multi-organ failure, rhabdomyolysis, deep vein thrombosis and sudden death. Fatality rate is high. Sudden reversal of fluid dynamics can lead from classic signs of hypovolemia to "flash" pulmonary edema within hours. Important differential diagnosis include sepsis syndrome (this is the most difficult to exclude, and it is recommended that empirical antibiotics treatment should be continued until the diagnosis is certain), anaphylaxis/angioedema, Gleich's syndrome (a.k.a. idiopathic hypereosinop[hilic syndrome, where cyclic edema is common, but usually associated with marked eosinophilia, elevated IgM levels, skin urticaria/lesions, encephalopathy and cardiac dysfunction possibly evolving into endomyocardial fibrosis), protein-losing enteropathy (diarrhea should be an important clue), nephrotic syndrome (massive proteinuria is diagnostic), acute pancreatitis, carcinoid/phaechromocytoma (skin flushing is an important clue). Treatment is largely empirical; it is important to closely monitor CVP and adjust fluid administration accordingly. Elements of acute therapy include: vasopressors (to maintain perfusion pressure), IV colloids (in preference to crystalloids), prostacyclin analogs (Epoprostenol is commonly used), theophylline/terbutaline (are of more benefit in the chronic/subacute state after the acute episode), and lately, attempts at immune modulation (Infliximab treatment appears promising).