Athens Kidney Center
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RETURN SERVICE REQUESTED

PITFALLS IN MANAGING FUNGAL DISEASES

Fungal disease is a disease of opportunity; it reflects the perturbed balance between "normal" endogenous microbial flora and opportunistic fungi acting in the context of a weakened host defense mechanism. Sources of fungal entry are: (a) endogenous GI fungi, (b) exogenous entry via instrumentation and catheters, (c) airborne spread/fomite handling for Aspergillus spp.

Isolation of fungi (colonisation) does not necessarily mean infection/disease: evidence of invasiveness and/or spread, are crucial to the diagnosis. Candida accounts for 8% of hospital infections, and is now the #4 most prevalent nosocomial infection, with mortality rates of 30-49%. Half of candida infections are C. albicans (the most virulent species, but also the most sensitive to "conventional" treatment); the other half are due to non-candida spp: in order of prevalence, glabrata (most common in elderly)> tropicalis (common in hematologic cancers/leukemia)> parapsilosis (most common growth over plastic surfaces, such as endovascular catheters, vascular prostheses, etc., and consequently at high risk for causing endocarditis) >krusei (innate resistance to azole antifungals).

Patients at high risk for fungal infections: (a) neutropenic, (b) malnourished/extended ICU stay, (c) chronic debilitation, (d) diabetics, (e) severe surface burns, (f) organ transplant recipients, (g) multiple breaches in skin/mucosal surfaces (especially in urologic or GI tract from instrumentation or disease), (h) multiple extended-use antibiotics, (i) patients on TPN, (j) treatment with steroids or cytotoxic drugs.

Fungal and other opportunistic infections are more common as a result of invasive (ICU) care, pervasive use of potent broad-spectrum antibiotics, chronic debilitation (in the elderly and from chronic organ dysfunction), immuno-compromise (from AIDS, cytotoxic treatment, post-transplantation immunosuppression).

Common management pitfalls: (a) low index of suspicion, (b) late diagnosis (therefore often disseminated at the time of diagnosis, leading to 30-49% mortality), (c) emergence of drug resistant strains (sustained by a culture of "half-hearted" or inappropriate treatment).

Drug treatment for acute fungal infections should last for at least 14 days after resolution of clinical symptoms/fever, and if chronic fungal disease, treatment should be extended for 6 months. Amphotericin B is the best option for neutropenic patients suffering from invasive fungal disease. As resistance to azole anti-fungal drugs is most common with C. krusei and C. glabrata, do not use azoles (such as fluconazole 400-800 mg IV daily) if those infections are suspected, but rather employ extended spectrum triazoles (such as voriconazole) or echinocandins (such as caspofungin) administered IV.

DEMENTIA: CLUES TO VASCULAR ORIGIN

Cognitive loss is common in the elderly, and is often assumed to be secondary to Alzheimer's disease. Not necessarily. At least 15% of dementias are from vascular disease, typically involving extensive small vessel disease. The 3 diagnostic clues are prior CVA (60% of stroke victims develop cognitive dysfunction apparent within 3 months), advanced age (which is not specific for vascular dementia) and presence of cardiac failure. Suggestive findings on evaluation include absence of early memory deficits, abnormal brain MRI findings, presence of post-stroke stigmata including focal neurologic lesions, clinical depression, nocturnal wandering/confusion, relative preservation of personality and emotional responses, urinary/fecal incontinence, increased somatization and emotional lability, and of course, the characteristic "step ladder" deterioration in cognitive function with intervals of extended neuro-stability.

WHAT IF IT DOESN'T WORK?

Treatment with pegylated interferon (IF) has become the standard of care for eliminating HBeAg and stimulating seroconversion to anti-HBe status in chronic hepatitis B infection. In a long-term surveillance study from Turkey, where HBV genotype D is common, a low response to IF was demonstrated: only 39% showed an initial response of cleared HBeAg antigenemia, with 84% of those later relapsing; in total, a dismal 9.8% of patients were able to show a sustained response to therapy (Senturk H et al, J Digestive Dis Sciences, 2010).

TREATING DVT IN CKD

The old assumption that DVT is uncommon in chronic kidney disease is wrong (Tveit et al, J Nephrology, 2002) and CKD patients have similar risk factors as the general population (Casserly et al, Am J Kidney Dis 2000). Indeed, age-adjusted risk for pulmonary embolism in ESRD patients is 2.3x that of the general population (Tveit et al, Am J Kidney Dis 2002) and an audit of autopsies performed in ESRD patients showed a startling prevalence of 12./4% for undiagnosed pulmonary embolism (Wiesholzer et al, Am J Kidney Dis 1999). Therefore, thrombotic risk is actually augmented in CKD probably as a result of the high prevalence of diabetes mellitus, pro-inflammatory status (highlighted by baseline elevation in CRP, fibrin degradation products, serum IL-6 levels, et cetera), hyper-homocysteinemia, pervasive platelet dysfunction and the vasculospastic effect of Procrit treatment. Data from ICU cases indicate that low molecular weight heparin is more effective (and less prone to provoking HIT) as DVT prophylaxis in high-risk patients (Geerts et al, ACCP Conference Statement, Chest 2004). Yet, because of concerns that LMWH may accumulate in kidney failure, heparin is still often employed as prophylactic of choice in this high-risk group. That fear should now finally be laid to rest. The DIRECT study did not show any increase in bleeding risk with dalteparin in CKD (Douketis et al, Archives Intern Med, 2008) and Tincani et al, Haematologica 2006 as well as Kani et al, J Critical Care 2006 both failed to demonstrate heparinoid drug accumulation in CKD. So folks, its OK to use LMWHs in CKD patients!

ICU DELIRIUM PREDICTS LONG-TERM COGNITIVE IMPAIRMENT

Delirium is an acutely evolved disorder of mood, cognition or behavior which is typically associated with inattention or altered perception, and characterized by a fluctuating clinical course. It could be hyperactive (overall best prognosis) or hypoactive (most easily misdiagnosed) or mixed (most common manifestation), and is now thought to represent imbalances in neurotransmitter levels, possibly involving the GABAergic pathways. Delirium is more common in those with dementia, and delirium itself is a common predisposing event towards dementia. Indeed, Francis & Kapoor, J American Geriatric Society, 1992, suggest that delirium is a marker of "impaired brain reserve", and therefore a reliable predictor of chronic brain disease or future dementing illness. Delirium in the ICU is predisposed by chronic disease (including hypertension, stroke or dementia), limited formal education, advanced age, history of depression or alcohol abuse, chronic smoking, severe illness (especially if intubation is required, or evidence of sepsis, electrolyte disturbances, organ failure, sleep deficits, hypoxemia or prolonged sedative use) and the apolipoprotein E4 phenotype. Experiencing delirium whilst mechanically ventilated in the ICU predicts long-term cognitive dysfunction in over 70% of survivors at 1 year post-discharge, which was reportedly severe in a third of those patients (Girard et al, Critical Care Medicine 2010). The longer the duration of ICU delirium, the greater the likelihood (and worse the severity) of later cognitive dysfunction. Additionally, delirium is associated with prolonged ICU stay, higher cost, higher re-intubation risk, and up to 3x higher mortality; these risks are cumulative, worsening with each additional day of delirium. Now, in addition to the known long-term sequelae of short-term ICU admission- clinical depression, post-traumatic stress syndrome, shortened longevity- we now have to add dementia (especially in those who experience delirium).

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SECOND OPINION

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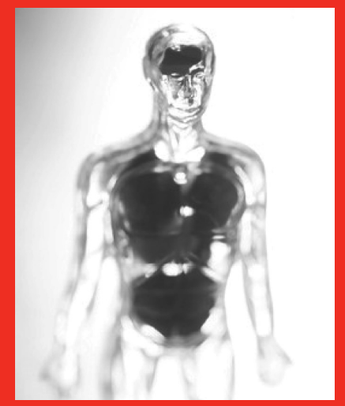
FROM THE EDITOR

Doctors are probably not given to much introspection. We lead busy lives, we are eye-witnesses to the cruelty of fate and disease, and our knowledge-base requires a constant renewal, as the new supersedes the old and discredited. Yet, every physician I know has at one time asked him/herself, why? Why do we dedicate our lives to what is essentially an impossible task, at the confluence of misery and death? Several reasons immediately assert themselves, but no contemporary writer in the medical tradition captures the transcendent- and elegiac- beauty of our tradition as clearly as Joshua Lederberg, formerly of the Rockefeller University: "for curiosity, the exercise of intellect and aesthetic taste; for virtuosity, the prestige and self-satisfaction inherent in the possession and practice of extraordinary skill; for power, the fruits of success being influence and vanity; for illumination, with its near-religious intensity, and for service by generating useful information and reaching other minds". Our raison d'etre is the dissemination of useful knowledge within our medical community, the philosophical underpinning of Daniel Webster's virtuous physician: competence and compassion. It is in that spirit that I welcome 2 new contributors, Rich Rosemund, MD and Jonathan Woody, MD., both are well representative of that ideal of medical virtuosity. Having closely worked with them over several years, I can attest that their clinical opinions have the force of ukase. Enough said. As always, I'll see you Friday, lunchtime at the CME lounge.

Beze Adogu, MD, Ph.D, FACP



AVOIDING ACUTE STROKES

The long-awaited INTERSTROKE trial report (O'Donnell MJ et al, Lancet, 2010) is out: analyzing acute strokes in 22 countries spread across 5 geographic regions and the entire spectrum of societal development (from advanced to developing economies), it identified 10 risk factors which account for 90% of all strokes, of which the top 5 risk factors account for 80% of all strokes. Those risk factors are uncontrolled hypertension, abdominal obesity (waist:hip ratio), sedentary lifestyle, cigarette smoking and poor dietary habits; the other risk factors are cardiac disease/atrial fibrillation, diabetes mellitus, alcohol indulgence (defined as >30 drinks q month), depression/psychosocial stress, and apolipoptotein B:A1 ratio. Not surprisingly, the risk factors from INTERSTROKE are very similar to the risk factors previously identified for acute myocardial infarction in the INTERHEART study (Yusuf S et al, Lancet 2004). Clearly, the study indicates that to avoid a stroke, it is most important to control arterial hypertension, stop smoking, and lose weight (especially around the abdomen). The other important findings are the nature of obesity as a risk factor (abdominal obesity is mote potent than BMI) as well as the predictive value of dyslipidemias (apolipoprotein levels trump LDL/HDL cholesterol values in importance). The next question will be: why do some people progress towards a stroke, and others end up with a heart attack?

USING THE BLUE PILL PROPERLY

In my practice, there are only 3 drug groups that patients often request without evident need or therapeutic suggestion: anorexigenic pills, narcotics or phosphodiesterase 5 inhibitors (Viagra, Levitra and Cialis, though never under their pseudonyms of Revatio or Adcirca, as currently marketed for treatment of pulmonary hypertension). The use of PDE5 drugs are destined to further expand with time.

The cautious physician should be aware of potential drug-drug interactions with these agents: inhibition of cytochrome P450 metabolism, typically through the 3A4 pathway (grapefruit, cimetidine, ketoconazole/itraconazole, antivirals especially the HIV protease inhibitors, particularly ritonavir); exaggerated vasodilation resulting in profound hypotension with nitrates and/or non-selective alpha-blockers (which block the alpha 1B receptor in the systemic vasculature, as with doxazosin/terazosin). Potential risks for prolonged QT intervals in conjunction with anti-arrhythmic agents or fluoroquinolone antibiotics, increased bleeding risk with anti-clotting agents, or alcohol-related orthostasis are theoretical considerations with limited clinical importance.

WHEN TO START ANTI-RETROVIRAL TREATMENT

Treating HIV- as with controlling hypertension or managing diabetes- has also become a moving target. Recent data culled from pooled, cohort observational studies in various countries by R. Lodwick et al, Lancet 2010, show that even without AIDS-defining illness, HIV-positive patients with a CD4 count above 350 (and in most cases, within normal levels) still have higher mortality rates than non-HIV positive patients. This difference was especially marked amongst IV drug users posting a mortality rate 9.3x higher than "normal", and least amongst homosexual male HIV patients (with a 30% increase above their "normal" peers). Mortality was lowest amongst the highest strata of CD4 counts. The reasons for the observed excess mortality are uncertain, though low-grade inflammation and persistent immuno-reactivity have been suggested as probable causes.

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AFTER A HEART ATTACK

First it was PROVE IT (Cannon CP et al, N England J Medicine, 2004), and now it is IDEAL (Pedersen TR et al, American J Cardiology, 2010): after a heart attack, you are much better off (reduced incidence of cardiocascular end-points of death, stroke, recurrent MI, unstable angina or revascularization surgery) with high-dose aggressive statin treatment. Are your post-MI patients on Lipitor 80 mg p.o. qHS for at least 5 years?

WHAT'S NEW IN UROLOGY

Robot-assisted cystectomy provides a minimally-invasive option to open radical cystectomy for bladder cancer. In a recent article, Michael Woods et al, Current Opinion in Urology, 2010, remind us of the advantages of robot-assisted cystectomy (reduced blood loss and RBC transfusion requirements, lower complication rates, improved convalescence times) but caution that medium-term and long-term outcomes are still unknown, and that results are surgeon-dependent (a reflection of the steep "learning curve" associated with robotic use).....talking of robots, Pruthi et al, reporting from University of North Carolina, studied references to robotic cystectomy on the Internet; not surprisingly, 61% of references were from providers, usually based at academic medical centers (who are often at the "cutting edge"), but alas, only 13% of information at those web-sites were factual, 7% were factual but inaccurate, 41% made no mention of outcomes data, 39% made wrong or unsubstantiated claims supporting robotic surgery, and only a dismal 5% of the claims made at such sites were evidence-based.....in a publication by Dan Moreira et al, Urology 2010, based on the SEARCH database, smoking is associated with more advanced prostatic cancer at surgery, and smokers with prostatic cancer tend to be younger, leaner, exhibiting more extra-capsular disease despite a lower prostatic volume, and have a higher pre-operative PSA level when compared to non-smokers; however, smoking, surprisingly, had little or no effect on risk of future biochemical recurrence of disease after surgery.....metastatic prostate cancer is a real bug-bear, nothing seems to work very well (though I concede, it still has a better prognosis than the notoriously refractory renal cell cancer) and preliminary data from the long-expected CALG-B study suggests that adding the anti-angiogenesis antibody, Avastia (bevacizumab) to the "traditional" regimen of Taxotere (docetaxel) and Predisone, did not improve outcomes but rather worsened mortality, morbidity (GI bleed, GI perforation, pancytopenias, hypertension) and cost of treatment.....but before you completely dismiss all monoclonal antibodies as lacking in value in Urology, recent data released at the American Society of Clinical Oncology meeting suggests that in metastatic prostatic cancer, denosumab administered SQ is superior to IV Zoledronic acid in delaying fractures and/or other clinical manifestations of metastatic bone secondaries.....coffee consumption does not increase the risk of prostate cancer, according to a recently released meta-analysis by Park C-H et al, British Journal Urology, 2010.....

VENOUS THROMBOLYTIC THERAPY

Deep venous thrombosis and pulmonary embolism have been identified as "signal" events in healthcare quality reviews, prompting the Center for Medicare & Medicaid Services (CMS) to label hospital-acquired DVT and/or PE as "never events". Still, in the United States, an estimated 600,000 cases of DVT/PE occur each year, resulting in about 100,000 deaths. The traditional treatment of venous thrombo-embolism consists of anticoagulation with unfractionated heparin with oral Coumadin. More recently, low molecular weight heparins have become the primary first-line agents, though patients with extensive ilio-femoral DVT are prime candidates for thrombolysis, inserting a catheter distal to thrombus and using guide-wire techniques to cross beyond the thrombus. Either mechanical or pharmacologic disruption of clot, using tPA, is available, and clot fragments can be safely aspirated. Sometimes, an unsuspected venous pathology may be discovered, such as the May-Thurner abnormality, where the right common iliac artery compresses the left common iliac vein, with resultant vein obstruction and clot formation. Stenoses are amenable to percutaneous transluminal angioplasty. Following thrombolysis, patients should be fully anticoagulated for at least 6 months. Catheter-directed thrombolysis should be considered for patients with extensive, acute proximal DVT with symptoms of less than 14 vdays duration, good functional status, low bleeding risk, and life expectancy >1 year (ACCP Guidelines, 2008). Absolute contraindications to thrombolysis include recent stroke/TIA, recent eye surgery, neurosurgical intervention, presence of intracranial tumor/bleed, seizures, surgery within previous 14 days or pregnancy; relative contraindications include advanced CKD, septic thrombophlebitis, uncontrolled hypertension, R-L intra-cardiac shunt, proliferative diabetic retinopathy, liver disease, active bleeding or GI bleed within previous 3 months. If in doubt, request a Vascular consultation. Jonathan Woody, MD (Vascular Surgery Program)

MULTI-DOSE VIALS AND INFECTION RISK

Using genetic analysis, the "point source" of the endoscopy-related hepatitis C virus infection epidemic in Las Vegas has been determined to be a contaminated multi-use vial of Propofol shared amongst various patients in different clinics, and not the endoscopy procedure itself or instrument contamination (Fischer et al, Clin Infectious Dis 2010). This unfortunate case with far-reaching medico-legal implications has resulted in the move to ban multi-dose vials from anesthetic use, as suggested by CDC investigators in a concurrent Gastroenterology editorial. Not to be outdone, the patient's attorney, Mr. Robert Eglet, has characterized multi-dose vials as "weapons of mass destruction" (Jane Feinmann, British Med J 2010).

REVERSING HEPARIN-INDUCED BLEEDING

Reversal of heparin anticoagulation is sometimes necessary to prevent exsanguination in the vulnerable patient. The most common reversal agent is Protamine sulfate, derived from fish sperm, which binds and neutralizes heparin. LMWHs are only partly bound by protamine (which is thought to be predicted by total sulfate anionic charge of the LMWH molecule), and hence, only partly reversed by protamine administration. 1 mg of protamine sulfate neutralizes 100 units of heparin or 100 anti-Xa units of LMWH (roughly equivalent to 1 mg of Lovenox). Caution should be exercised in protamine-allergic patients, who might have been sensitized to protamine from historical use of PZI insulin in the 1960s. As the elimination half-life of heparin is 60-90 minutes, administration of protamine after 4-5 half-lives (i.e. 5-7 hours) of heparin administration is probably of no value.

FETAL ARRHYTHMIAS

The normal fetal heart rate is about 2x adult rate, i.e. 120-160/min. Arrhythmias occur in ~1% of all fetuses, the vast majority being extrasystoles (75%), the most common subtype being premature atrial contractions (PACs). Tachyarrhythmias account for 15% whilst bradyarrhythmias account for only 10% of fetal arrhythmias. Diagnosis often rests on pulse irregularity (usually irregularly irregular) on auscultation, with ultrasonographic evaluation for structural heart disease.

PACs are characterized by 1:1 conduction from the atria to the ventricles, followed by a compensatory pause after each extrasystole. Parents can be reassured that this is a benign arrhythmia, which usually resolves spontaneously. It is important to avoid provoking factors, including drugs such as caffeine and nicotine. About 1% or less may deteriorate into either a tachy/bradyarrhythmia, as detected by periodic cardiac auscultation. That finding should warrant immediate referral to a materno-fetal medicine specialist, and frequently entails a cardiology referral.

Fetal SVT is diagnosed when there is 1:1 conduction from the atria to the ventricle, typically with a rate between 240 and 280/min, which can either be sustained or intermittent. When this abnormal pattern is observed less than 50% of the time, it is usually well tolerated by the fetus, and does not lead to hydrops fetalis. However, immediate treatment should be offered for sustained SVT or where there are signs suggestive of impending hydrops and/or in situations where fetal maturity is compromised. Treatment consists of digoxin as first line regimen; because fetal drug concentrations are generally lower than maternal levels, and the volume of drug distribution is much higher in pregnant patients, large loading doses of digoxin are often necessary in order to achieve therapeutic levels. Mild to moderate maternal digitoxicity may precede any therapeutic digitalis effect on the fetus. The second-line drug is flecainide, which also has pro-arrhythmic effects. In cases of refractory SVT or where signs of cardiac decompensation are evident (e.g. tricuspid regurgitation, enlarged cardiac chambers, hydrops fetalis) immediate delivery is indicated.

Atrial flutter is seen with an atrial rate of 300-500 with variable atrio-ventricular block. This abnormal rhythm is usually more refractory to treatment, tends to be sustained, and is more likely to be associated with underlying structural heart disease. Treatment is similar to that for SVT.

The most common pathologic cause of sustained fetal bradycardia is complete heart block (CHB). This is associated with congenital heart disease; indeed, where no structural cardiac defects are noted, bradycardia is almost always seen with anti-cardiolipin antibodies, such as anti-Ro/La antibodies in SLE, Sjogren's syndrome, or other connective tissue diseases. These antibodies inhibit cardiac repolarization by selectively binding to the fetal myocardium. Complete heart block occurs in ~1% of mothers with positive anti-cardiolipin antibodies. The results of treatment using maternal administration of steroids have been mixed. Current recommendations dictate weekly cardiac auscultations between weeks 16-24 for patients with positive anti-Ro/La antibodies. If fetal bradycardia cannot be demonstrated during that period, it is unlikely to occur during the rest of the pregnancy. Monitoring fetal arrhythmias during labor is difficult at best, and most of the time cesarean delivery is recommended because of an inability to determine normal fetal heart rate patterns as typically seen in well-oxygenated, healthy fetuses. Treatment of the neonate in the nursery can then be initiated directly with much greater success, as therapeutic drug levels are more easily and consistently attained. Rich Rosemund, MD (Materno-Fetal Medicine & High Risk Pregnancies)

FOR DEBATE: TIMING CAROTID ENDARTERECTOMY IN CABG PATIENTS

A recent review by R. Naylor, J Cardiovascular Surgery, 2009, addresses this controversial topic. Multiple trials have shown that CABG is of proven benefit in coronary artery disease; stroke is an important cause of peri-operative morbidity and mortality in CABG patients (who, as we now know, following the CAPRIE study, actually have similar arterial stenotic vascular lesions elsewhere); carotid endarterectomy/angioplasty is of proven benefit in advanced carotid artery stenosis; incidence of peri-operative (especially post-operative) stroke in CABG patients is high enough in selected populations to warrant prophylactic carotid intervention. However, it is unclear if carotid artery disease is the prime or even an important cause of post-CABG strokes, and there is still no evidence that prophylactic carotid endarterectomy/angioplasty is of net benefit in post-CABG patients (because of the high procedural morbidity of carotid intervention). Therefore, carotid intervention in the CABG candidate can only be justified based on current knowledge if proven carotid stenosis is associated with history of prior TIA, prior infarctive stroke, bilateral severe carotid disease, but is not justified for asymptomatic unilateral carotid stenosis. If a stroke has already occurred, immediate surgery following ictus risks the conversion of an ischemic zone into a hemorrhagic field with resultant extension of infarctive penumbra. Previous studies showed that carotid endarterectomy immediately after a stroke was associated with 5.1% risk of another stroke, but drops to only 1.6% if surgery is delayed (Rockman et al, J Vascular Surgery, 2006) though the figures from more contemporaneous studies suggest that early interventions are equally safe (Ballotta et al, Surgery, 2002). The consensus is that maximum surgical benefit is achieved when intervention is closest to a recent neurologic event (Rothwell et al, Lancet, 2004), noting that ~20% of strokes attributed to carotid artery disease recur, with 30% of such recurrences in first 30 days of "signal" stroke. The optimal staging method is equally uncertain: staged carotid artery intervention preceding CABG vs reverse staging of CABG preceding carotid artery intervention vs synchronous CABG with carotid surgery at the same time. More studies will be coming down the line.

ANGIONEUROTIC EDEMA

Angioedema, an acute, non-immunologic, non-pruritic swelling of the skin and submucosal tissue, primarily involving the face and pharynx, has become a more common clinical finding since the advent of ACE inhibitors and ARB drugs. Angioedema may be provoked by aspirin, contrast dye challenge, NSAIDs, calcium channel blockers, penicillins, and foods (such as peanuts). In practice, 25-40% of all angioedema seen in the ED result from ACE inhibitor or ARB therapy. Indeed, 0.12% of all ALLHAT trial participants experienced angioedema, and 0.40% of lisinopril-treated hypertensives developed this potentially fatal complication, a finding which appears to be 5x more common in Black patients. The pathologic basis is inhibition of bradykinin degradation in tissue, resulting in localized vascular permeability, sub-mucosal edema and capillary leakage; the added impact of high tissue levels of substance P, histamine and C1 esterase is unclear. Patients of Asian descent are more likely to present with cough than overt laryngeal edema.

REVERSE EPIDEMIOLOGY OF HYPERTENSION IN KIDNEY FAILURE

We've heard of the J-curve, the U-curve, and now comes the W-curve....Rajiv Agarwal, Hypertension 2010, reports that systolic hypertension, a well known risk factor for premature cardiovascular death in most populations, has an unusual prognostic value in dialysis patients. Previous studies had shown that low pre-treatment blood pressures were predictive of death within the first 2 years in dialysis patients, a finding thought to reflect the high prevalence of heart failure, autonomic dysfunction, sepsis/systemic vasodilation and use of multiple CVS medications amongst this group. That phenomenom was referred to as "reverse epidemiology" to denote its reciprocal relationship to findings in "normal" non-dialysis populations. Other studies later showed that systolic BP was predictive of LV hypertrophy and cardiac failure, and more intriguingly, after 3 years on dialysis, systolic hypertension was once more predictive of premature CVS death. Agarwal's study confirmed that BP recordings taken during dialysis treatment (which we obsessively perform every 15 minutes, thank you) had no predictive or prognostic value (in other words, we probably shouldn't bother); that BP readings taken outside dialysis treatments had a W-shaped relationship to outcome; that manual BP measurements routinely overestimate "true" BP readings, and therefore, a finding of low BP using a manual instrument was particularly auspicious for poor outcomes; good BP control was related to long-term improved outcomes.

DOSING TRANSPLANTED KIDNEYS

Just as we all suspected, the future of kidney transplantation will probably include a means of "sizing" kidneys prior to organ allocation. A French study by Magali Giral et al, J American Society Nephrology, 2010, report that a low donor kidney weight: recipient total body weight of <2.3 g/kg was associated with a 55% higher risk of early post-transplant kidney failure. Such mismatched kidneys were liable to develop higher rates of proteinuria, higher BP levels in recipients, higher prevalence of focal sclerosis/scarring in transplanted kidney, and ultimately, a faster rate of disease progression in transplant. Moral: large patients need large kidneys.

WHO WOULD HAVE THOUGHT THAT?

Marta Canfield et al, J Addiction Medicine, 2010, report in a study of hospitalized patients undergoing treatment for opiate addiction that 73% of such addicts first came into contact with opiates through prescription drugs. About 41% of those had legitimate prescriptions from their doctors, whilst 32% had diverted the legitimate prescriptions of others. Only 27% picked up the drug habit from the "streets". With time, addicts tend to gravitate towards use of IV heroin, primarily because of its more pronounced clinical effects. Moral: is your next well-meaning prescription for Lortab PRN the "gateway" drug down the spiral of addiction?

PROLONGED QT INTERVALS

The risk of prolonged QT (defined as QT above 450 msec, though its pathologic significance is dependent on both ambient heart rate and gender, hence the need to correct for heart rate) is triggered polymorphic ventricular tachycardia or torsades de pointes. Notable risk factors for prolonged QT include bradycardia, ion channel polymorphisms, electrolyte abnormalities (hypokalemia, hypomagnesemia), female sex, digoxin treatment, cardiac failure, anti-arrhythmic drug therapy (especially the class Ia and III drugs), opiate use (but not associated with morphine or Ultram). Over 65 drugs are known to prolong QT via various mechanisms, principally by prolonging repolarization through blockade of the rapid component of the delayed rectifier Ik channel; less common mechanisms include enhanced inward sodium currents, reduced expression of functional (K) channels, et cetera. Common causes of QT prolongation in the hospital include chlorpromazine, narcotic drugs/opiates, haloperidol, chlorpromazine, Bepridil (for angina/CAD) and antimicrobials (such as Erythromycin, Biaxin and anti-malarials). Proper management should incorporate: (a) early identification of "at risk" patients (prior treatment with proarrhythmic drugs? low pulse rate? electrolyte changes?) + (b) correction of modifiable risk factors + (c) close QTc/EKG telemetry monitoring (d) immediate DC cardioversion (to terminate arrhythmias/torsades lasting above 5 sec) + (e) slow IV bolus of Magnesium sulfate + (f) increase ambient heart rate >100/min (either with IV isoproterenol infusion or transvenous pacing) + (g) consider cardiac defibrillator/permanent pacemaker (based on potential risk of recurrence).

LEST WE FORGET

Hypertension is common: the adult prevalence in the US is now 37%. How low should treat hypertension go? The data which we reviewed several months ago suggest a J-type relationship between systolic BP levels and long-term outcomes, especially in coronary artery disease. Messerli et al, Annals Intern Med 2006, show that optimal systolic BP was 120-130 mmHg in CAD patients. Cooper-DeHoff et al, Circulation 2007, using the INVEST data-base, confirmed that poor outcomes were common in the elderly with CAD under 120/80 mmHg.

DEPARTMENT OF DANGEROUS DRUG COMBINATIONS

Periodically, this section will highlight some commonly used drugs that could, in combination, result in potentially dangerous adverse effects. By highlighting some of these potential problems, we hope to lessen the risk of therapeutic misadventure in the office or at your clinic.

1. Plavix + PPI = acute coronary syndrome: the rationale is that Plavix is a pro-drug which is converted to its active metabolite by cytochrome P450 (CYP2C19), an enzyme system that is blocked by PPIs, and thereby blunts the therapeutic effectiveness of Plavix. The safest PPI in this scenario might be pantoprazole (Protonix).
2. SSRI + Aspirin = excessive (GI) bleeding: the rationale is that SSRIs also block serotonin reuptake in platelets, causing profound serotonin depletion and failure of platelet aggregability.
3. Digoxin + macrolide Antibiotics = impaired digitalis metabolism resulting in digitoxicity: the rationale is that digoxin is partly metabolized by GI bacterial flora (including the anerobic bacillus, Eubacterium lentum) which results in higher bioavailability of digoxin (and higher serum digoxin levels) following antibiotic clearance of endogenous flora. A similar mechanism explains why antibiotics augment the anticoagulant effects of coumadin (or conversely, by disrupting the entero-hepatic cycling of estrogen metabolites, typically lessen the effectiveness of estrogen pills, resulting in contraceptive failure).