Athens Kidney Center
1440 North Chase Street
Athens, GA 30601

RETURN SERVICE REQUESTED

POTENTIAL PITFALLS IN MANAGING LACTIC ACIDOSIS IN THE ICU

Last week, a 54 y.o. diabetic WF presented to the ICU with profound lactic acidosis due to metformin toxicity, tissue hypoxia (from respiratory compromise) and acute renal failure. She survived. Her hospital course reminded me of potential pitfalls in managing type B lactic acidosis (i.e. lactic acidosis not primarily attributed to tissue hypo-perfusion, hemoglobin transfer disorders or cardio-pulmonary failure resulting in increased lactate generation, but is rather due to reduced lactate clearance from uncoupling of oxidative phosphorylation principally due to liver/kidney failure, malignancy, medications or alcohol excess).

1. Immediate focus on hemodynamic stability is crucial; adequate amounts of IV fluids should be administered and vasotonic medications avoided, if possible.
2. The apparent volume of distribution for metformin is estimated at ~3 liters/kg, suggesting significant intracellular accumulation.
3. Therefore, if dialysis is performed, dialysis-induced hypotension and/or hypovolemia must be avoided (to avoid increased lactate generation from tissue hypoxia), and duration of dialysis should be extended rather than using high-intensity treatment (to more efficiently "clear" the intracellular compartment).
4. Sodium bicarbonate is an efficient buffer of acid moieties and can help maintain hemodynamic integrity; however, it also increases lactate synthesis via net CO2 production. Animal experiments suggest that Carbicarb is a safer acid buffer, and dichloroacetate is equally effective leading to improved lactic acid levels, though survival is not altered in controlled trials.
5. IV epinephrine as well as neo-epinephrine (Levofed) can provoke or worsen lactic acidosis through tissue hypoxia.
6. Metformin incites lactic acidosis by mitochondrial cytopathy (i.e. direct mitochondrial toxicity) which may demonstrate person-to-person variability in susceptibility as a result of genetic polymorphisms in miotochondrial DNA.
7. Any role for supplementing co-factors of the mitiochondrial respiratory complex IV chain is unproven, but few case reports support addition of vitamin B supplements, L-carnitine and co-enzyme Q10.
8. Avoid other drugs that could provoke lactic acidosis, especially those that cause mitochondrial cytopathy (anti-HIV reverse transcriptase inhibitors, tetracyclines, linezolid, propofol anesthesia) or increase pyruvic acid generation (beta-2 agonists) or induce hepato/nephro-toxicity (aminoglycosides, isoniazid, IV contrast).
9. Propylene glycol is the solvent for nitroglycerine, phenytoin and lorazepam (and can be metabolized into lactic acid).
10. Suggestive CT findings are common in lactic acidosis, and though ischemic bowel syndrome is an important consideration, there have been several reports of "non-diagnostic" CT findings which typically resolve after correction after lactic acidosis.

WHAT HAPPENS AFTER THE ICU?

With intensive medical care, critically-ill patients are more likely to survive life-threatening illness. However, a recent study by Hannah Wunsch et al, *JAMA* 2010, shows that ICU stay is a marker for poor long-term survival, at least amongst Medicare beneficiaries (i.e. patients older than 65 years). Using a Medicare data-base, they found that a third of patients were re-hospitalized within 6 months of ICU discharge, a sixth of survivors died within 6 months of discharge, rising to almost 40% by 3 years after discharge. Mortality was particularly high amongst ICU patients who were intubated, discharged to a nursing home or were diagnosed with metastatic cancer.

WHEN TO RECONSIDER CPR

CPR is a common and popular hospital procedure, though its benefits may have been exaggerated: it provides hope (which is often transitory) in extreme cases, it gives an illusion of "masterly activity", it keeps hospital staff busy, it is distressing to family onlookers, and it sometimes works. The question is deciding who it best works for, and how "aggressive" it should be.

A meta-analysis by Cohn et al, *J General Internal Medicine*, 1993 and more recently by Reisfield et al, *Resuscitation*, 2006, now provide us some guidelines. In general, the elderly, those with severe underlying chronic illness (such as metastatic cancer and pervasive renal failure) or chronic inanition do not do well, and generally die before planned hospital discharge. On the other hand, CPR following an acute myocardial infarction has 1 of the best correlations with long-term survivability, again providing support that sudden cardiac death after acute coronary syndromes is often from an electrical (and not a pump) failure.

J-CURVE IN DIABETES MELLITUS

Nothing has been the same since ACCORD (ACCORD Study Group, *N England J Medicine*, 2008) showed that tight glycemic control could be deleterious. A recent study by Craig Currie et al, *Lancet* 2010 from the General Practice Research Database suggests that hemoglobin A1c of 7-7.5% was optimal, oral hypoglycemic agents were agents of choice, and hypoglycemia must be avoided or aggressively treated.

the SECOND OPINION

June 2010 *A monthly medical newsletter for the Athens medical community* Volume 1, #6

FROM THE EDITOR

Finally, it came to pass, as was published in the journal, *Science*, last week. Craig Venter had finally arrived at the conclusion of his 15-year odyssey. Man- in this case, Dr. Venter- in his endless pursuit of happiness, liberty and the limits of credulity, has created life. Not re-created, but created; not a pastiche from a laboratory cook-book, not an approximation of independent biologic existence, but a true genomic sequence capable of reproduction and serial propagation. We are, after all, the sum total of all our genes. At long last, an artificial life form has been built from scratch using chemicals, and of course, the deft hands of molecular medical technology. The realm of creation, once the sole preserve of the gods has now fallen to human hands: we have begun to annex the kingdom of God.

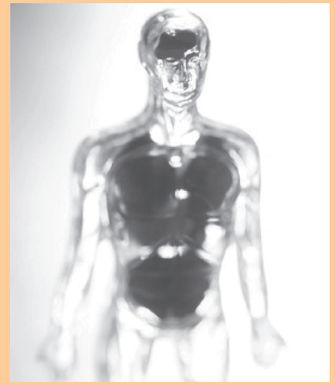
In the beginning, if you believe the Greeks- who, as the Creteans would tell you, are known to lie about things like this- there was Chaos. From that endless emptiness arrived Gaea, the earth mother, who gave birth to Uranus, the deep blue sky. In quick and rather ungodly succession, they gave birth to the awesome Titans, followed by the noisome Cyclops, before lapsing into consanguineous strife. History, as was to be demonstrated over and over again in the coming age of Man, repeats itself, with Gaea abetting the insurrection of Cronus against his father, a crime which would be later visited on Cronus himself by his wife, Rhea, acting out her maternal instincts through the baby Zeus. With time, Zeus himself, distracted as much by his libido as his patricidal instincts, failed to notice that Prometheus, a liberal Titan if ever there was one, had surreptitiously passed on the gift of fire to mankind, with the unintended consequences of suborning arson, creating a new age of felony, and tellingly, making it possible for man to adopt the very peculiar distinction of being the only animal that deliberately inhales smoke. In a fit of Olympian pique, Zeus drowns mankind in a flood of biblical proportions, condemning the Promethean enabler to relapsing liver necrosis and cyclic regeneration whilst chained to Mount Caucasus. Implausibly, as with all other creation myths, the origins of the First Being or creator remained obscure.

Based on this *Science* publication, we no longer have to invoke parthenogenesis to explain how life began on earth: life can, ostensibly, come from a chemical reaction under the right set of conditions. Even though it runs contrary to our aesthetic zeitgeist, we do not need to invoke a creator to explain the miracle of life. Me? I readily confess that I am still partial to the creation myth of Genesis, as well as the heroic saga of the genderless and fearsome *Olodumare* in the Yoruba creation tale, as well as several other fascinating creation myths from the many primitive races of mankind, each description no less apocryphal than our prescribed reading of Genesis. And now, having finally created life, it is perhaps time for the esteemed Dr. Craig Venter to take a bow. Even if this isn't his 7th day. Even if his created bacterium is yet to been sanctified. Even as I stand with Virgil: *Fictio cedit veritati*.

At this end of the genetic code, our task as physicians is to keep already created human life intact and sacrosanct. Our higher purpose in ennobling creation is unchanged. But as men, we will endlessly ponder and debate the implications (and unintended consequences) of this new leap into the frontiers of creation science. We wait with bated breath.

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

Beze Adogu, MD, Ph.D, FACP



Contents Within:

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

ANEMIA IN HEART FAILURE

The relationship between anemia and outcomes (including mortality) in heart disease as in chronic kidney disease (CKD) is non-linear. A J-type relationship has been demonstrated in the general population (Gagnon et al, *American Heart J*, 1994), acute coronary syndromes (Sabatine et al, *Circulation*, 2005) and congestive cardiac failure (Sharma et al, *European Heart J*, 2004). As with CKD, most excess risk is at the lowest hemoglobin levels, but optimal hemoglobin appears to be 13-16 g/dL in heart failure and 10-12 g/dL in CKD. It has been suggested that anemia may be a marker for chronic illness, mediating neuro-humoral activation, left ventricular hypertrophy/remodelling and a pro-inflammatory state, whilst erythrocytosis may mediate blood hyperviscosity and other adverse rheologic effects on blood flow.

FUTURE OF SEPTIC SHOCK THERAPY?

Sepsis is a common ICU event, and gram-negative endotoxemia is a recognized harbinger of death. The EUPHAS trial by Cruz et al, *JAMA* 2009, was prematurely discontinued based on the reported low mortality amongst septic shock patients randomized to be treated with polymyxin B extracorporeal hemoperfusion, which removes circulating endotoxin by adsorption.

IN CASE YOU MISSED IT

We often use serum PSA levels to monitor or help diagnose prostatic neoplasia. Dr. Chang and colleagues at Stanford report that some commonly prescribed drugs can reduce serum PSA levels over time, in some instances accounting for up to 25% drop in serum levels over 5 years. The culprits are: NSAIDs, statins and thiazide diuretics. These effects appear to be synergistic, and could be abrogated by concurrent use of calcium channel antagonists.

UNDERSTANDING UROSEPSIS

1. The diagnosis of UTI depends on presence of *symptoms* (dysuria, flank/suprapubic pain, frequency, fever/chills, incontinence) plus laboratory confirmation of *significant bacteriuria* (i.e., greater than 100,000 colonies per mL of mid-stream clean-catch urine sample, where at least 80% of isolates are from the dominant bacterial species): when time is of the essence, a positive *nitrite test* can substitute for a colony count, but note that the nitrite test has high specificity at 96% (and a positive predictive value of 88%) but lower sensitivity, being unable to detect non-reducing bacteria which do not elaborate reductase enzyme, and therefore cannot convert nitrate to nitrite (such as gram-positive cocci including enterococci and staphylococci, Pseudomonas and mycobacteria).
2. Leucocyte esterase test reflects the presence of (hydrolyzed) WBCs in the urine and not necessarily an infection; this test is positive in any situation associated with leucocyte infiltration within the kidneys: trichomoniases, bacterial vaginosis, kidney stones, vasculitis, peri-renal abscess and acute (allergic) interstitial nephritis from drug hypersensitivity. Conversely, even in the presence of severe urosepsis, this test may be negative in neutropenic patients as well as when the esterase hydrolytic reaction is impaired from glycosuria (diabetics) or proteinuria (nephrotic syndrome) or hyperoxaluria (small intestinal disease).
3. Most UTIs are from *E. coli* and other gram-negative aerobic bacteria such as *Klebsiella* spp. In kidney stone disease and other situations associated with an alkaline urine pH as well as in male patients, *Proteus and Morganella* spp. often predominate. Following long-term antibiotic treatment, *enterococci* superinfections are common (as is candiduria, more so if indwelling urinary catheters are used: treat by first removing the catheter, which resolves 33% of candiduria). In in-patient hospital settings, multi-drug resistant isolates of *Pseudomonas*, *enterococci*, *Serratia*, *Citrobacter* and *Acinetobacter* are commonly found. Generally, *streptococci*, anerobic bacteria and *lactobacilli* do not propagate in urine, therefore isolation of any of these organisms in urine represents a contamination.
4. Asymptomatic bacteriuria is common in the elderly, does not progress to kidney injury, and is typically intermittent showing spontaneous clearance without treatment; treatment neither changes outcome nor prognosis: Doctor, Do Not Treat.

NEPHRECTOMY IN FAILED RENAL TRANSPLANT

Return to dialysis following failed renal transplantation is associated with excessive mortality. A recent paper by Ayus et al, *J American Society Nephrology*, 2010, showed that amongst post-transplant ESRD returning to dialysis, allograft nephrectomy was associated with a 32% lower risk of death. This paper extends the work of Johnston et al, *American J Transplant*, 2007, which had previously shown that late nephrectomy (after 12 months of transplant failure) was strongly associated with reduced mortality but paradoxically, a higher risk of repeat "secondary" transplantation failure.

BEFORE UNIVERSALLY ADOPTING SUBCUTANEOUS ERYTHROPOIETIN THERAPY

With "payment bundling" just around the corner, thoughts have sharply veered towards strategies for cost-containment in dialysis care. There is evidence that subcutaneous erythropietin administration leads to a slower and sustained rise in blood erythropoietin levels in sharp contrast to the spikes noted with IV treatment. Therefore, the erythropoietic effects of subcutaneous dosing are thought to be more pronounced, translating to lower drug costs. A study from Korea by Lee Young-Ki et al, *American J Kidney Diseases*, 2009, confirms that the subcutaneous route is also associated with a 3.5x higher risk access failure, presumably triggered by the thrombogenic and vasculopathic effects of ESAs.

NON-MOTOR SYMPTOMS OF PARKINSONISM

Parkinson's disease is a slowly progressive, common (but often undiagnosed), neurodegenerative condition afflicting ~1% of the elderly, and is characterized by the classic signs of rest tremor + akinesia + rigidity + postural instability. Non-motor features may predominate or pre-date those classic signs, and may help the busy practitioner detect an otherwise "occult" case of parkinson's disease, especially when these "cluster" in the older patient: features of cognitive impairment, impulsive/compulsive behavior, depression, apathy and hallucinosis; autonomic dysfunction with impotence, constipation, dysphagia, dysgeusia, drooling, orthostasis, heat/cold intolerance and bladder irritability; loss of smell sensation; sensory neuropathy, excessive fatigue, seborrhea (greasy "mask like" facies is typical) or unexplained pain; sleep disorders including insomnia, restless legs syndrome, vivid dreams, daytime somnolence and unrefreshing sleep.

USE OF BNP TO TITRATE CHF CARE

B-type natriuretic peptide (BNP), an autocoid neuro-hormone secreted by cardiac myocytes in response to ventricular distension, is a useful aid in diagnosis of volume overload. Low levels predict better long-term outcomes in CHF, and reflect adequate treatment with cardiac-effective medications such as beta-blockers, loop diuretics, ACE inhibitors and aldosterone blockers. In a meta-analysis, Porapakkham et al, *Archives Intern Medicine*, 2010, show that CHD treatment titrated to BNP levels was associated with reduced all-cause mortality in patients younger than 75 years compared to "usual clinical care" without BNP-guided titration, but surprisingly, did not significantly affect hospitalization risk. It was hypothesized that this advantage from BNP-titration may reflect the ease of achieving recommended drug doses for CHF management. This beneficial effect was lost in the very elderly, who also tend to have higher BNP levels, most probably because of the higher prevalence of co-morbidities, drug-induced hypotension, and treatment-related pre-renal kidney failure.

ELEVATED LFTS DURING STATIN THERAPY

Elevated levels of transaminases are present in 8% of the adult population, being a marker for sub-clinical liver disease (attributed to non-alcoholic steatohepatitis, hepatitic B/C infection, alcoholic hepatitis, autoimmune hepatitis, drug toxicity and hemochromatosis) and often preceding statin exposure. As statins are often associated with *transient* elevations in serum transaminase levels without concrete signs of liver toxicity or failure at low doses of statin use, it has been suggested that this finding may reflect increased hepatocyte membrane permeability and enzyme leakage without pathologic liver damage. If transaminase levels are less than 3x normal, continue statin treatment and recheck levels in 6 weeks whilst searching for other causes of liver damage; if transaminase levels are over 3x normal, it is advisable to hold statins until resolved, and then consider re-challenge at lower statin dose (Russo et al, *Cleveland Clinic J Med* 2004; Calderon et al, *Mayo Clin Proceedings*, 2010).

DIABETIC NEUROPATHY

Diabetic neuropathy is common (life-time prevalence of 25-50% in all diabetics: Dyck et al, *Neurology*, 1993) and under-diagnosed (75% with diagnostic findings were not formally diagnosed, and 56% of sufferers do not know what the term means: ADA position paper, *Diabetes Care*, 2007). Any diabetic with distal loss of perception (initially to vibration as tested with a 128 Hz tuning fork) or distal paresthesias/allodynia (which is typically worse at night) or bilateral motor weakness very likely has neuropathy. It is important to consider less common causes of neuropathy in the diabetic, especially vasculitis/autoimmune disorders, hypothyroidism, paraneoplastic syndromes, medications (nucleoside analog anti-HIV drugs, cytotoxics and platinum-based drugs, hydralazine, amiodarone, colchicine, Flagyl, heavy metal exposure) and uremic neuropathy. Treatment does not aim to *abolish* pain but to substantially reduce pain/distress and restore function. Effective strategies include optimized glycemic control, Lyrica/pregabalin (start at 25 mg p.o. TID and increase up to 100 mg p.o. TID, except in renal failure), Cymbalta/duloxetine (start at 20 mg p.o. q daily to obviate nausea, and titrate up to 120 mg p.o. q daily), Neurontin/gabapentin (100 mg p.o. TID to 1200 mg p.o. TID: Backonja et al, *JAMA*, 1998), other anti-depressant drugs (primarily TCAs such as Elavil/amitriptyline and SNRIs such as Effexor/venlafaxine), alpha-lipoic acid (some but not all trials support adding 600 mg p.o. q day to reverse pathologic changes of neuropathy: Ziegler et al, *Diabetes Care*, 2006), topical Zostrix/capsaicin C applied QID (takes up to 3 weeks to induce analgesia by depleting substance P, which re-accumulates if drug is withdrawn for over 24 hours), topical 5% lidocaine (Barbano et al, *Arch Neurology*, 2004), topical nitroglycerine spray to extremities (Yuen et al, *Diabetes Care*, 2002) and Ultram/tramadol 50 mg p.o. q daily titrated up to 400 mg p.o. q daily (the role of opiate analgesics in neuropathic pain is controversial).

INTUBATION SANS SEDATION

To reduce the adversity associated with over-sedation in the ICU, Strom et al, *Lancet* 2010, report a new protocol for mechanical ventilation without active continuous sedation, using 2.5-5 mg IV morphine as boluses on a PRN basis at a single center in Denmark. Though continuous combination sedative-analgesic therapy is thought to reduce distress and oxygen consumption in intubated patients, there is data to suggest over-use resulting in extended failure-to-wean as well as other medical morbidity such as ventilator-associated pneumonia, GI bleeding, cholestatic jaundice, DVT, chronic sinusitis and post-traumatic stress disorder. This randomized trial supports a reduced ICU stay with minimal sedation protocol without added adversity, except for increased haloperidol-responsive agitated delirium.

MICROCYTOSIS IN ANEMIA

Anemia with low MCV is likely to be iron deficiency, especially in "high risk" groups: minorities, low socio-economic status, postpartum status, recent blood loss/donation, vegetarians, women with high menstrual flow, and obese children. Such patients would also have a low ferritin level (except if suffering from concurrent illness, as ferritin is an "acute phase reactant" just like ESR), low iron saturation and high total iron binding capacity (except if severely undernourished).

Other considerations in microcytic anemia are: sideroblastic anemia + thalasemia + anemia of chronic disease + chronic lead poisoning.

Iron is efficiently absorbed from the jejunum, a process which is impeded if iron is provided in non-heme diet (green vegetables rather than red meat), acidity is buffered by PPI or anti-histamine drugs, or binfers chelate iron (especially cereals, bran and other phytates, as well as tea, coffee and other tannates).

PITFALLS IN MANAGING ACUTE PANCREATITIS

A 48 y.o. WM was admitted with presumed gallstone-induced necrotizing pancreatitis to the ICU. He expired. It is important to review management guidelines for this high-fatality illness based on current knowledge.

1. Aggressive IV fluid resuscitation is imperative: patients are more likely to receive sub-optimal amounts of fluid than be over-hydrated.
2. Most cases are due to alcoholism or gallstones: less than 15% are due to trauma, hypercalcemia, post-operative status, hypertriglyceridemia, infections (mumps, typhoid and streptococci), medications (sulfa drugs, diuretics, estrogens, tetracyclines and valproic acid)
3. Serum amylase/lipase are useful to making a diagnosis but have no prognostic value; daily or serial levels are not necessary, except to help interpret a clear change in clinical status.
4. High serum amylase levels may be from other causes, therefore consider other causes in unexplained "secondary rise" of amylase levels: uremia, peronitis/GI perforation, mesenteric infarction, cholecystitis, DKA, ruptured ectopic pregnancy, salivary gland inflammation/tumors and macroamylasemia (macromolecular complex of amylase-serum protein which is too large for normal glomerular filtration).
5. Most cases of pancreatitis are mild, even sub-clinical; 15% of hospitalized patients have severe disease, which is life-threatening and often associated with multi-organ system failure, "third spacing", pancreatic necrosis (which should be confirmed with CT scan, showing non-enhancement in >30% pancreatic mass with IV contrast) and shock.
6. There is no substitute for careful daily physical evaluation: several scoring systems are in current use, including the Ranson criteria, Atlanta scoring criteria, the 5-point BISAP score, and APACHE II score. All are complicated. The important thing is to search for evidence of systemic inflammatory response syndrome (SIRS), organ dysfunction (cerebral, pulmonary, cardiac, liver or renal) or infection.
7. Antibiotics are not needed in mild cases, but are of benefit as prophylaxis in necrotizing pancreatitis or empirical treatment for suspected infection: lipophilic antibiotics (e.g. Primaxin IV or quinolone-Flagyl combination) with excellent tissue penetrance and adequate anerobic coverage are recommended.
8. Infection from necrotic pancreatitis can only be proven by fine needle aspiration, not by fever (or other signs of SIRS): if positive, antibiotic selection should be based on culture results, and consider surgical/endoscopic debridement of necrotic tissue.
9. Hemorrhagic pancreatitis may be suggested by ecchymoses around umbilicus or at flanks.
10. Counteract the catabolism of severe pancreatitis by early initiation of either parenteral nutrition or passing of nasojejunal tube (which does not stimulate the pancreas).
11. Retained stone as cause of progressive biliary pancreatitis (often with picture of ascending cholangitis) may be suspected from serologic data (elevated cholestatic liver enzymes such as alkaline phosphatase and "direct" bilirubin), dilated bile duct on ultrasonography, identification of stone by MRCP/endoscopic ultrasonography: refer for ERCP (and as in all cases of gallstone pancreatitis, refer for cholecystectomy within 6 weeks of ictus to prevent recurrences).