Athens Kidney Center
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ACUTE LIVER FAILURE

Abrupt liver failure is uncommon, clinically heterogenous but with a uniformly poor prognosis. We are often faced with acute liver failure in the ICU setting, often as part of multi-organ failure in ischemic hepatitis ("shock liver"); however, by far the most common cause of acute liver failure in United States is drug-induced, with Tylenol overdose being the major culprit (other etiologic drugs include idiosyncratic reactions to NSAIDs, antibiotics and anti-convulsants). Elsewhere in the world, viral hepatitis is still the most common cause. Less common causes are pregnancy, Wilson's disease and Budd-Chiari syndrome; about 15% are "idiopathic" and it is thought that a significant proportion of those are actually due to Tylenol use. It is important but challenging to exclude acute-on-chronic liver failure (as may occur with acute flares of chronic hepatitis B infection, autoimmune hepatitis and Wilson's disease), and that distinction may never be made until a liver biopsy is done. Death is related to etiology (idiosyncratic drug reactions do worse than direct Tylenol hepatotoxicity), rapidity of evolution (if time from jaundice to encephalopathy is under 1 week that presages a fair prognosis, but if over 1 month in evolution that implies an abysmal prognosis), presence of dyscoagulopathy (PT >100 sec), cerebral edema, infection/sepsis, encephalopathy (especially grade III or IV), acute kidney injury (especially if serum creatinine above 3.4 mg/dl), extremes of age (children and elderly fare particularly badly) and persistent acidosis despite adequate fluid resuscitation. Those benchmarks have been put together as the King's College prognostic criteria (does anyone still remember Dame Sheila Sherlock?).

Now comes a paper indicating that routine administration of N-Acetylcysteine (which repletes liver glutathione) in all cases of acute liver failure has prognostic advantages even in those without obvious Tylenol-induced liver failure (Lee et al, *Gastroenterology* 2010). There were no differences in short-term survival between those receiving Mucomyst and placebo in non-Tylenol acute liver failure, but survivors who received Mucomyst generally did better.

DIABETIC FOOT INFECTION

Diabetic foot infections (and ulcers) are common, deadly and misdiagnosed. About 20% of diabetics develop pressure necrosis at the heels/metatarsal heads, leading to foot ulcers. About 20% of those ulcers become infected, leading to contiguous bone spread (osteomyelitis). Any deep foot ulcer in a diabetic should be presumed infected, and probably osteomyelitis. To confirm the diagnosis, look for the following: visible or exposed bone in ulcer crater; ESR >70 mm/hr; localized bone lucency with cortical erosion/loss of trabecular pattern on plain X-ray (periosteal "reaction" or bone sclerosis are late findings) noting that sensitivity is only 20-70% and takes at least 2 weeks to show structural bone changes; focal area of reduced signal intensity on MRI usually in bony cortex (sensitivity 80-100%); triple phase Tcm99 bone scan (too sensitive for routine use, and only 45% specificity, often showing increased uptake from fractures, degenerative arthritis, cellulitis, etc); tagged WBC scans are less sensitive and less specific than MRIs therefore used as substitute in resource-poor settings; CT scans do not appreciably improve on plain X-ray findings; bone biopsy is critical in refractory infections or suspected multi-drug resistant strains.

IN CASE YOU MISSED IT

Severe sepsis/septic shock is a high fatality illness: the most common cause of death in non-coronary ICUs. Current definition is based on the ACCP/SCCM Consensus criteria of suspected/proven infection + 2 or more SIRS criteria + infection-related organ dysfunction +/- systolic BP <90 mmHg despite adequate fluid resuscitation. Mortality is over 50%, and with kidney failure rises to 70%. Not much has changed by way of outcomes in 30 years. New findings might finally shed light on this "black box".

1. Adequate fluid resuscitation prior to, or at the very least, within 6 hours of vasopressor treatment as a bolus of 20 mL/kg or more to achieve a CVP of at least 8 mmHg followed by conservative fluid replacement (targeted at even or mildly negative fluid balance) thereafter, is superior in preventing acute lung injury (and further renal compromise) compared to overly liberal fluid treatment (Murphy et al, *Chest* 2009).
Another article of interest on the same problem suggests that overly aggressive fluid replacement was linked to worse outcomes in the critically ill, with each 1% increase in fluid overload leading to 3% increase in mortality (Sutherland et al, *American J Kidney Dis* 2010).

2. Diastolic dysfunction as demonstrated by Doppler wave imaging can be used as a discriminant marker of outcomes far more reliably than elevated cardiac biomarkers (Sturgess et al, *Critical Care* 2010).

3. We know that use of low-dose steroids in severely septic adults is of potential benefit, but adding intensive insulin treatment to control hyperglycemia does not confer added benefits (COIITTS Study investigators, *JAMA* 2010).

4. Adjunctive use of fludrocortisone to help reverse hypotension in severe sepsis was not beneficial (ibid).

5. Using the RIFLE classification of acute kidney injury (Risk, Injury, Failure, Loss, End-Stage) Gordon et al, *Intensive Care Medicine* 2010, showed that vasopressin IV was better than norepinephrine IV in preventing progression of early kidney failure and was also associated with better survival outcomes in septic patients.

6. Development of acute lung injury/ARDS leads to hypoxemic pulmonary failure with high pCO2 levels, which might accentuate systemic/cerebral vasodilation and lead to cerebral edema. It is important to resist the temptation of increasing tidal volume but attempt higher mean airways pressure and PEEP (despite the residual risk of barotrauma).

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SECOND OPINION

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FROM THE EDITOR

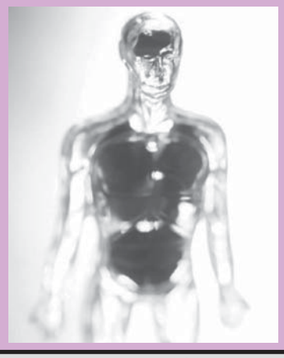
Science, as with medicine, strives for truth. There is a tacit assumption that published articles (especially in high-brow medical journals) represent "original" truth- truth of the unvarnished, existential kind- that is, gospel truth. Not necessarily. The point is that whilst truth itself is objective, its perception remains humanly subjective. As doctors and scientists, we have all battled with the nuances of truth, and our interpretations often subvert the deeper significance or clinical implications of our findings. Just like gospel: it was our own interpretations of biblical truth that helped fuel some of the carnage in medieval Europe. It was our cataractal perception of the centrality of man (and by necessary implication, his earthly abode) that led to charges of apostasy leveled at Galileo and early renaissance thinkers.

It is fortunate that science- and medicine- can change its mind. It does not necessarily dismiss earlier observations, but reflects a more complete appreciation of fact. Altered medical opinion does not impute chicanery or fecklessness; we ought to be custodians of fact, not of opinion or ego. Not too long ago, I was relentlessly proselytizing for dual ACE inhibitor plus angiotensin receptor blocker therapy in my kidney patients. Then, I was standing firmly on the COOPERATE trial by Nakao et al, *Lancet* 2003. Times have changed. Since the publication of ON TARGET, I have had to eat my words. I suspect I am not the only doctor with egg on his face. There will be other *volte face* renunciations of previously held dogma in coming years. However, changes in clinical practice ought to considered, and we should not be inveigled into serving as mouthpieces for corporate pharmaceutical interests. New data must be critically reviewed, and inherent biases ferreted out. Published truth should not become kabuki theater, statistical sleight-of-hand masquerading as harlequin.

One might recall that with the introduction of tobacco to the Western world, the inscrutable Nicolas Monardes, MD, in 1571 published at least 36 different ailments that could be prevented or cured by smoking. That memorable list included halitosis, gout, gingivitis, cancer, ague, and- believe it or not- syphilis (the French disease, if you speak English; the English disease, if you speak French). It took the magisterial intervention of King James I, to put an end to such preposterous nonsense. He reminded his more gullible subjects that any link between syphilis and tobacco was akin to an old harlot attributing her longevity to harlotry: both are at best, coincidental. Good old King James, who by the way was not beholden to the tobacco industry, was able to separate the social concerns of licentiousness from the pharmacologic challenge of tobacco use. If Dr. Monardes had limited his list to parkinsonism and inflammatory bowel disease, who knows, we might still be celebrating his otherwise incomparable medical talents to this day.

Despite a more sophisticated understanding of cause and effect, our interpretation of unrelated observations/events as mere happenstance, coincidence or pathogenesis remains vestigial. If we are mystified by the ever-changing explanations offered in medical opinion papers, imagine the consternation of the laity: How tightly should we control diabetes? How low should treated blood pressures run? Should we cardiovert in atrial fibrillation? How do we prevent (talk less of treat) acute lung injury in the ICU? Welcome to the new world of fast-paced medical knowledge. Fasten your seat belts- this ride could get bumpy pretty quick. All said, I'll see you Friday lunch-time, at the CME lounge.

Beze Adogu, MD, PhD, FACP



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WHEN TO COMMENCE DIALYSIS?

Nobody knows the optimal time to initiate dialysis. New data suggests that the best time is not "early". Despite old observational and non-randomized trials supporting early initiation of dialysis for CKD on the grounds that it led to better outcomes, recent studies have contradicted that idea (Lassalle et al, *Kidney International* 2010). Mining the REIN database- a gift that apparently keeps on giving- investigators found that those with higher eGFR at initiation of dialysis had shorter survivals. This anti-intuitive finding actually corroborates more recent trials, but the reason might be because of the associated (cardiac) co-morbidity implicit in "hurried" dialysis inception. Conclusion: starting dialysis should be individualized for each patient, but there should be no "rush" by nephrologists to commence dialysis treatment.

PROGNOSTICATION IN HYPONATREMIA

Clinicians have relied on the traditional classification of hyponatremia as hypovolemic vs euvolemic vs hypervolemic, to enable clinical diagnosis. Now, a new study uses a new classification of hyponatremia as community-acquired vs hospital-acquired vs hospital-aggravated (i.e. community-acquired hyponatremia worsening during hospital admission) to enable improved prognostication (Wald et al, *Archives Intern Med* 2010). Based on this classification, community-acquired hyponatremia accounted for 38% of hyponatremias and was associated with a 52% higher risk of in-hospital death, 12% higher risk of discharge to a rehabilitation/nursing facility, and 14% longer hospital duration. Hospital-acquired hyponatremia accounted for another 38% of hyponatremias, with a 66% higher risk of fatality, 64% higher risk of rehab/nursing home discharge, and 64% longer hospital course. Hospital-aggravated hyponatremia was the most malignant, developing in 6% of community-acquired hyponatremias and resulting in 2.3x higher death rate.

TREATING POST-SURGICAL ILEUS

Medicine has become increasingly pro-active with respects to post-operative ileus. Following surgery, failure of intestinal peristalsis is common, and may preferentially affect the stomach (gastroparesis), small bowel or colon. Ileus is more common in females, the elderly, diabetics those with electrolyte deficits, following extensive/manipulative bowel surgery, and in patients exposed to narcotic analgesics (which inhibits colonic transit via its effect on peripheral mu-opioid receptors).

New strategies to prevent or shorten post-operative ileus include:

1. Laparoscopic surgery, which is less traumatic to bowel tissue.

2. Limit use of nasogastric suction tubes which is associated with higher infection rates/atelectasis and longer time to resumption of oral feeds (Cheatham et al, *Ann Surgery* 1995) except in cases of refractory vomiting or inability to protect airways (to avoid aspiration).

3. Consider early institution of enteral feeds within 24 hours of surgery using nasojejunal or nasoduodenal tube (Lewis et al, *J Gastrointestinal Surgery* 2009).

4. Simulate early feeding by gum-chewing which is thought to stimulate vagal efferents (Purkayastha et al, *Archives Surgery* 2008).

5. Consider thoracic epiduiral anesthesia for peri-surgical pain control (Zingg et al, *Surg Endoscopy* 2009).

6. Metoclopramide (Reglan) which stimulates gastric emptying and blocks the dopamine D2 receptor is effective only for gastroparesis.

7. Alvimopan (Entereg) which blocks the mu-opiod receptor is helpful in small bowel ileus if started pre-operatively and continued orally for 3-7 days.

8. Neostigmine (Prostigmin) which reversibly inhibits acetylcholinesterase (increasing its effect at the acetlcholine muscarinic receptor) is effective as an IV infusion in colonic ileus.

9. Erythromycin which is a macrolide antibiotic also stimulates the motilin receptor and is useful when given IV for gastroparesis only.

HYPERURICEMIA: THE ART OF SHOOTING AT A MOVING TARGET

Hyperuricemia is, by definition, serum urate >6.8 mg/dL, the physiological saturation threshold for uric acid, above which monosodium urate monohydrate comes out of solution as crystals, leading to gouty arthritis, tissue tophi or kidney stones/disease. This disease is getting more common each decade, afflicting an estimated 2% of the adult population. The most common underlying cause is reduced urate excretion by the kidneys (which is typically from a multifactorial defect in the urate anion re-absorbtion mechanism in the proximal tubules, either from genetic factors, alcohol use, chronic kidney disease, diuretic use, low-dose ASA or niacin therapy). Less common causes include high purine diets (rich in meat, seafood, fructose-containing beverages), increased cell turnover (classically as occurs in tumor-lysis syndrome) and mutations involving rate-limiting enzymes in purine metabolism (most notoriously in the Lesch-Nyan syndrome). Hyperuricemia is a common finding amongst the elderly, and is particularly high in those with cardio-metabolic syndrome, diabetes mellitus, CKD, heart disease, or on any of the medications listed above.

Treatment of hyperuricemia has been advocated because of epidemiologic data suggesting a causal link between "asymptomatic" hyperuricemia and vascular/cardiac disease. Treatment involves:

1. Low purine diet, which is onerous and impractical, and only lowers serum uric acid by 1 mg/dL.

2. Anti-arthritic remedies such as NSAIDs, short-dose steroids x 3-5 days, colchicine 0.6 mg p.o. given q 1-2 hours until either 6 mg cumulatie dose or onset of diarrhea or resolution of symptoms.

3. Allopurinol, which is a renally eliminated xanthine oxidase inhibitor, ought to be dosed on a TTT (treat to target) formulation as outlined by Perez-Ruiz et al, *Arthritis Rheum* 2008: start low at 100 mg p.o. daily and increase dose to maximum of 800mg/day or until target serum uric acid level is attained (usually at or below 4 mg/dl to effect tophi "debulking"); beware of allopurinol hypersensitivity syndrome which is particularly common in CKD, those on concurrent thiazide diuretics, and possibly, those with HLA B58 (more so for skin reactions, which include Stevens-Johnsons syndrome and toxic epidermal necrolysis).

4. Febuxostat (Uloric) which is a hepatically eliminated xanthine oxidase inhibitor is more expensive but much better tolerated than Allopurinol.

5. Uricosuric agents block the urate anion reabsorbtion pathway in the proximal tubules, and could theoretically precipitate uric acid crystals within renal tubules; their clinical use has declined significantly in recent years. Drugs with uricosuric properties include probenecid, benzbromarone, losartan (and possibly other ARBs) and fenofibrate.

6. Uricase is elaborated from other mammals (or isolated from fungi, as in the case of rasbucase, which only has a limited span of effectiveness of under 12 months); uricase drugs isolated from other mammals are intensely immunogenic, and current attempts to reduce immunogenicity by drug pegylation are undergoing phase III clinical trials.

RECOGNIZING HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin use is universal, being administered in at least 25% of hospitalized and virtually 100% of hemodialysis patients as the short-term anticoagulant of choice. Though it has been recognized since 1958, diagnosis and treatment of HIT is often confusing. Let us review the main clinical facts:

1. HIT describes a clinical syndrome attributed to heparin exposure and incorporating 1 or more of 5 manifestations: thrombocytopenia (typically mild to moderate, generally above 20,000/mcl), thrombosis (most commonly venous, but includes myocardial infarcts, limb ischemia, DVT and pulmonary embolism), venous limb gangrene (especially in those with very high INR levels from concurrent oral warfarin treatment, and presumed coumadin-induced protein C inhibition), skin necrosis (at injection sites) and acute systemic reaction (usually within 30 minutes of IV administration and presents as acute dyspnea, chills, cardio-pulmonary collapse, chest pain, shock or febrile reaction: this may be misdiagnosed as an anaphylactoid reaction).

2. Pathogenesis of HIT is dependent on exposure of neo-epitopes on platelet factor 4 following conformational changes after heparin-platelet factor 4 binding; this is followed by elaboration of pathogenic IgG antibodies to the neo-epitopes, and consequent platelet activation by IgG-heparin-platelet factor 4 complex.

3. HIT typically occurs between 5 and 15 days of heparin exposure: if the patient had previously received heparin within the last 100 days, HIT could occur earlier; if patient has a high titer of platelet-activating IgG antibodies development of HIT could be slower.

4. Diagnosis depends on a high index of suspicion (in heparin-treated patients presenting with either low platelet counts, bleeding or clotting complications) plus confirmation of IgG HIT antibodies (either using an immunologic ELISA-based assay or less commonly, 14C-serotonin release functional assay) plus reversal of thrombocytopenia within 2 weeks of heparin removal.

5. Only IgG antibodies appear to be pathogenic, though IgA and IgM antibodies have been isolated from patients; the ELISA antibody test is very sensitive at ~95% but lacks specificity at ~50-95%; even "homeopathic" doses of heparin can provoke HIT- therefore exclude use of

RECOGNIZING HEPARIN-INDUCED THROMBOCYTOPENIA *(Cont.)*

all heparin, even heparin-coated syringes/catheters; HIT is more common with unfractionated heparin but can occur with LMWH; bovine heparin appears more pathogenic than porcine heparin.

6. The best option for non-heparin anticoagulation is employing direct thrombin inhibitors: lepirudin is very immunogenic and is renally-cleared, therefore could provoke bleeding complications in CKD patients; argatroban is not immunogenic but is hepatically-cleared, therefore used with caution in liver failure, and also significantly raises INR therefore making coumadin transition more problematic.

7. For dialysis patients, recent attention has focused on regional citrate dialysis and catheter packing with sodium citrate.

DIABETES CONTROL: INTENSIVE OR CONSERVATIVE?

Diabetes mellitus is a common cause of premature death, primarily through cardiovascular attrition. Optimal glycemic control is essential, as it reduces the vascular burden of long-term complications. What is unclear is the degree to which euglycemia should be pursued, especially during acute illness. Both oral medications as well as insulin have significant side-effects including weight gain, cardiac dysfunction, hypoglycemia and acute metabolic complications such as lactic acidosis. Several new trials are helping reshape clinical opinion. In summary, while the data for long-term benefits with "tight" control appears robust, in the short term, that strategy is typically prone to misadventure especially amongst the non-surgical critically-ill. This conclusion appears to be consistent with findings from the ACCORD (*N England J Medicine* 2008), ADVANCE (*N England J Medicine* 2008)and VADT (Duckworth et al, *N England J Medicine* 2009) trials.

1. Lingvay et al, *Diabetes Care* 2009 showed that over 3 years, tight control with either triple oral hypoglycemic agents (sulfonylurea + metformin + proglitazone) or insulin-metformin combination was associated with superior outcomes and lack of "secondary" failure of glycemic control (presumably from progressive glucotoxic beta-cell dysfunction) in treatment-naive type 2 diabetics.

2. UKPDS trial supports intensive treatment with either sulfonylureas or insulin or metformin though each model was associated with progressively worsened glycemic control over time (from gradual pancreatic beta-cell damage following onset of clinical diabetes).

3. The oft-forgotten classic by van den Berghe et al, *N England J Medicine* 2001, had shown in a prospective, randomized controlled study that intensive insulin treatment in intubated patients within a surgical ICU resulted in a 42% reduction in mortality.

4. The trial that changed our ICU protocols was the NICE-SUGAR study which compared intensive vs. conservative glycemic control in general ICU patients; it found a higher incidence of cardiovascular deaths and a 13-fold higher risk of severe hypoglycemia in the "intensive" insulin group, but no significant differences otherwise (NICE-SUGAR Study Investigators, *N England J Medicine* 2009).

5. As no medical controversy is ever complete without a meta-analyses, Wiener et al, *JAMA* 2008 found no difference in overall mortality between intensive and conservative insulin treatments in the ICU, whilst Langley & Adams, *Diabetes Metab Res Rev* 2007 found a difference in their own set of comparative trials.

7 CORE GUIDELINE MEASURES IN CARDIAC MANAGEMENT

Cardiac disease and chronic renal disease share the same stratum ("soil")of underlying causes including arterial hypertension, diabetes mellitus and progressive vascular disease. Unfortunately, patients with CKD are routinely excluded from cardiac trials, and there is a body of evidence that they are systematically under-treated with respect to their cardiac disease. Data from the IMPROVE-HF database supports the pervasive low adherence to management guidelines for CKD patients: as renal function decreases, treatment with ACE inhibitors/ARBs also drops- similar (but less dramatic) declines were noted for the use of beta-blockers and aldosterone antagonists (Heywood et al, *Am J Cardiology* 2010). Sadly, the use of other core recommendations (anticoagulants, heart failure education, resynchronization therapy, implantable cardiac defibrillator) were uniformly less likely for all CKD patients. Who would have thought that CKD was a contraindication to heart failure education?

HYPOKALEMIA: IS IT REALLY BARTTER'S?

Everyone remembers the classic features of Bartter's syndrome: childhood onset of spontaneous renal salt-wasting associated with hypokalemic chloride-resistant metabolic alkalosis, typically with normal BP levels, elevated plasma renin activity and high serum aldosterone. There are 4 major phenotypes of Bartter's: types I and II having an antenatal onset with fetal polyuria, polyhydramnios and retarded growth (type I is caused by a defective Na-K-2Cl co-transporter, type II by a defective K-channel); type III sometimes manifesting with mild hypomagnesemia (because of a chloride channel defect in the distal convoluted tubule as well as the thick ascending limb of Henle's loop); and type IV being associated with sensorineural deafness (attributed to multiple defective Cl channels). Generally, the Bartter's patient is metabolically equivalent to the surreptitious user of loop (Lasix) diuretics. Not all "Bartter-type" hypokalemia is Bartter's syndrome. It is important to evaluate for hypomagnesemia and mirror-image hypermagnesuria, which might expose a previously undiagnosed Gitelman syndrome.

Gitelman syndrome is autosomal recessive, manifests in adolescence or even adulthood (not childhood, as in Bartter's) and results from a mutation affecting the thiazide-sensitive sodium-chloride co-transporter at the distal convuluted tubule. The Gitelman patient behaves like a surreptitious abuser of thiazide diuretics!

CLUES TO DIAGNOSTIC PUZZLE

Case: 38 y.o. Black immigrant of Angolan ancestry presented with disseminate tuberculosis despite negative BCG test on a recent pre-employment physical evaluation. He was started on anti-tubercular chemotherapy. He had a syncopal episode 3 weeks later, and was found at the ER to be severely hyponatremic, mildly hypotensive (BP was 99/50 mmHg), with urine Na of 43 mmol/L and serum Na of 109 mmol/L.

Question: Was this SIADH from pulmonary tuberculosis, drug-induced hyponatremia (from rifabutin or capreomycin or ethionamide) or an Addisonian crisis? Could it be cerebral salt wasting syndrome? What further tests are needed? Should I empirically use hypertonic saline? What are your thoughts?

QUO VADIS?

First, a study out of Pakistan showed that vitamin B supplementation reduced albuminuria in diabetic nephropathy (Rabbani et al, *Diabetologia* 2009). Which was interesting, as high homocysteine levels had been shown to be associated with vascular (and progressive kidney) disease. Next, it was shown that vitamin B was demonstrably effective at reducing plasma homocysteine levels. Then, it turns out that reducing homocysteine levels did not necessarily alter your vascular risk. Now comes yet another bombshell, hot from the play books of evidence-based medicine: supplementation of vitamin B actually worsens kidney decline and is associated with a higher risk of vascular events in diabetics with CKD (House et al, *JAMA* 2010). Go figure!